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1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
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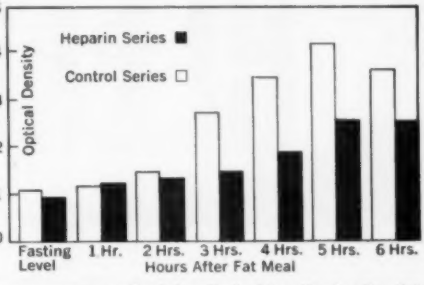

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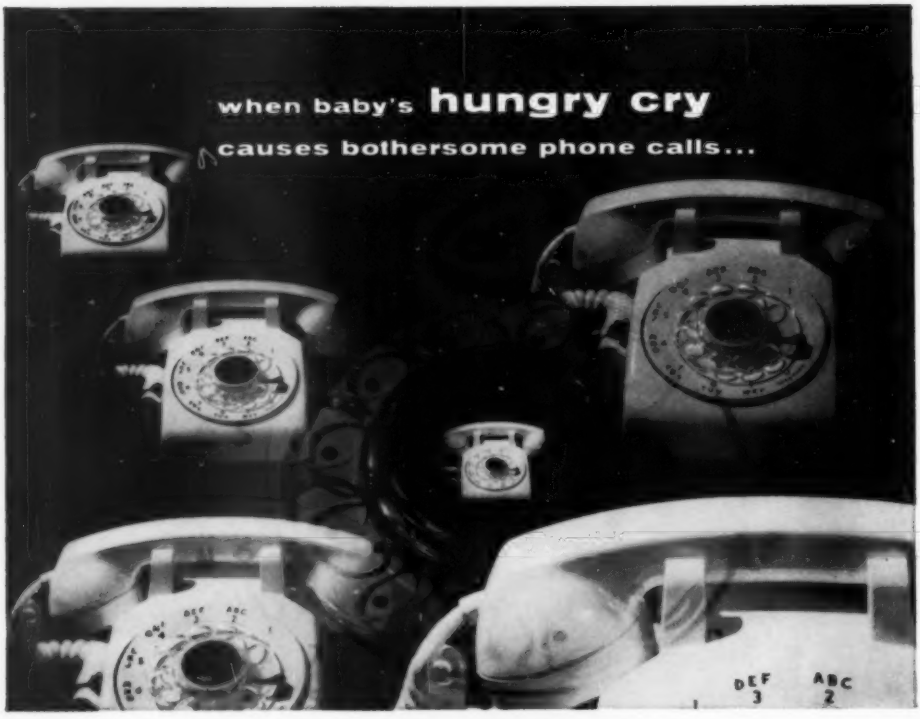

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1. Hatfield, M. A., Simpson, R. A., and Jackson, R. L.: J. Pediat. 44: 32-45 (Jan.) 1954. 2. Frost, L. W., and Jackson, R. L.: J. Pediat. 39: 585-592 (Nov.) 1951. 3. Henrickson, W. E.: GP 8: 51-56 (Oct.) 1953. 4. Litchfield, H. R.: Arch. Pediat. 61: 617 (Dec.) 1944.

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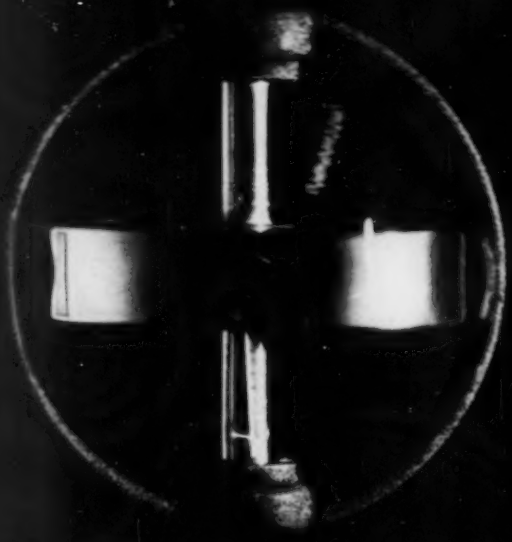

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*Carter, S.: *M. Clin. North America*: 315 (March) 1953.

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1. Council on Drugs: Penthienate bromide, In: New and Nonofficial Drugs 1958, Philadelphia, J. B. Lippincott Co., 1958, pp. 255-256.
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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CLINICAL ASPECTS OF AGING CONNECTIVE TISSUES*

EDGAR M. BICK

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THE connective tissues of the human body take part in the structure and function of all its separate organs and locomotor mechanisms. Notwithstanding this obvious fact, remarkably little attention has been paid to connective tissue as an organic system beyond the pages of descriptive anatomy and the chemistry of its ubiquitous component, collagen. This has been quite unfortunate, since in many areas it plays a conspicuous part in the nature of deformity and dysfunction following the protracted disability of prolonged disease or the acute disability of trauma.

Amid all the attention paid to the contraction of muscles in postpathologic states, their intricate relationship to perimuscular and intramuscular fascia rarely if ever has received the notice it merits. A convincing thesis might be written reviewing the musculoskeletal deformities generally ascribed to "muscle-contraction" and discovering the common misnomer. Only in recent years, for example, has the effect of contraction of the iliotibial band on pelvic and spinal deformity, or the adherence of infraquadriceps fascia to the periosteum of the femur, been properly appreciated. In many such instances it will be found that

* Presented in part at the combined meeting of the Section on Orthopedic Surgery of The New York Academy of Medicine and the Philadelphia Orthopaedic Club, March 9, 1959.

the muscle itself is quite extensible, and the restraining factor to be rather the resistances or adhesions of associated connective tissues.

In considering the effect of traumatic lesions of the locomotor apparatus in the elderly, the influence of certain factors inherent in aging connective tissue is especially pertinent[1]. The ease with which their limbs stiffen and the commonly experienced difficulty of regaining an adequate range of motion after any severe trauma, in spite of the generality of an atrophic musculature, make it desirable to know more about the natural course of aging in the involved connective tissue elements.

In previous essays, the well known age changes in the musculoskeletal apparatus have been discussed[2, 3]. However, during the preparation of the relevant material it became apparent that little of significance had been published regarding concurrent changes in human connective tissue in persons of advancing years. Some work has been done on the elastin fibers of blood vessels[4, 5], and other studies have been directed at the connective tissue fibers of the skin[6]. The latter are of chief interest to dermatology and perhaps to the problems of plastic surgery. There are a number of reports easily available describing age changes in the chemistry of collagen[7-9]. As yet, however, these chemical studies have offered little of clinical significance. Studies on pure connective tissue in the aged have been conspicuously absent.

In order to understand the difference in the functional capacity of the connective tissue system at different ages, it is first necessary to study the structural changes found in aging persons. Observations on gross material have proved quite unrewarding. When human connective tissues of the locomotor apparatus of the elderly are examined at the operating table, the individual fasciae, bands and capsules appear no different to sight or palpation than comparable examples in the younger adult. They are as firm, as glistening and apparently as unworn in a healthy person of 80 years as in one of 20. It would be of considerable importance to be able to test their resiliency *in situ* by physical means, but this would necessitate some degree of detachment from their tissue beds and thereby introduce distorting variables of immeasurable degree.

Therefore the first study in this project was aimed at the structural histology of the musculoskeletal connective tissues. In order that observations be kept comparable, sections were examined from a similar structure of each individual. A strip of human fascia lata was taken from

a group of patients ranging in age from 13 to 89 years, who were undergoing surgical intervention for lesions not directly involving this tissue. Sections of each of these specimens were treated with several special stains and were studied as parallel series. It was observed that the musculoskeletal or pure connective tissues are remarkably stable and that little change ordinarily occurs until quite an advanced age is attained. However, the change which then occurs proved to be of very considerable interest to the clinical problem of rehabilitation of the elderly. These data have been separately recorded[10].

To summarize the findings, it was noted that there were no perceptible changes in the cytology of the specimens nor was any significant variation observed in sections stained for collagen by the usual van Giesen method. This latter was to be expected and may or may not be significant, since there is no satisfactory stain for demonstrating the structural aspects of collagen fibers. An attempt to search for changes in the mucopolysaccharide content of aging fibers, by employing the Schiff stain for periodic acid, was equally unproductive. The only specific change noted in the sections of the older age group was found in the elastic fibers, marked for the purpose by the Verhoef stain. These showed a strong though variable tendency toward coarsening and fragmentation.

This manifestation of the aging process, as is true of structural changes occurring in all parts of the body with advancing years, is never uniform. It is variable in each specimen, being prominent in certain fields and absent in others. Just as white hair, cartilage degeneration or vascular sclerosis appears gradually and unevenly, so also does the degeneration of elastic fibers in the musculoskeletal connective tissues. But in all specimens of the aged group, compared with those of adults under 60 years, the changes are definite and usually appear to increase with advancing years.

The structural changes having been observed, their application to certain clinical problems of the aged becomes obvious. Any traumatic lesion of the locomotor apparatus must of necessity involve, directly or indirectly, some part of the connective tissue system. The end-result of the treatment of a fractured hip, even when union has been successfully obtained, owes at least part of its speed of functional recovery to the relative elasticity of the joint capsule, the juxta-articular ligaments and fascia lata. Fracture of the lower third of the femur inevitably involves

its anterior periosteum and overlying subquadriceps fascia. If these two connective tissue planes become adherent or involved in the reparative callus, the extent of subsequent knee function will depend to some degree on the elasticity of their uninvolved portions. Similar examples may be drawn from all fractures of the long bones, and the most persuasive instances are those associated with fractures at or in the vicinity of the articulating surfaces of these long bones.

It has been repeatedly noted that while uncomplicated compression fractures of the vertebrae ordinarily cause no great disability, the response of the spinous and paraspinous ligaments to such injury in the aged often conditions the nature of the postfracture subjective complaints[3]. Persistent strain of the less elastic dorsolumbar or lumbosacral ligaments and fascia are almost characteristic of vertebral fractures in the elderly, frequently at levels other than that of the fracture itself. It is common knowledge that healed fractures about the shoulder take far longer to regain an acceptable range of motion in the aged than they do in younger adults, and conversely, it is not an uncommon experience to find that mechanical measures designed to hasten such recovery in the younger group may even retard it in the older.

Following muscular trauma in the aged, for example, a severe contusion about the anterior tibial or calf muscles, so-called "muscle stiffness", is often unduly prolonged. Similarly, simple ankle sprains, tendon sheath inflammations, self-reduced traumatic subluxations of the fingers and such traumata elsewhere in the locomotor apparatus, ordinarily require a considerably longer recovery period in the aged than do similar lesions in the younger age groups.

Retardation in functional recovery following fractures or injuries to the soft tissues of the locomotor apparatus is seen to occur in spite of the fact that within the boundaries of clinical perception, in an otherwise healthy elderly person, broken bones unite as rapidly as in younger adults[11], and wounds heal as quickly[1, 12]. It therefore becomes necessary to assign the fault to other factors.

It would be absurd to offer any one item as a simple common denominator for the retardation of functional recovery of the locomotor apparatus in the aged. Vascular, neural, endocrine, metabolic and especially emotional factors all play a part. The present writer has attempted only to add one more rather neglected element to the list. The gradually decreasing elasticity of the connective tissues of the musculo-

skeletal system also adversely influences functional recovery of the locomotor apparatus from trauma or from prolonged disabling illness from any cause. Unlike several of the other retarding factors mentioned, however, this last may be gainfully influenced by the proper conduct of rehabilitation procedures. Like the others, it may also be adversely affected.

It has been generally believed for some time that, while collagen and collagen fibers reproduce themselves throughout the life of the organism, elastin fibers, when once destroyed, do not[10, 13]. This, of course, is the basis of the relative inelasticity of scar tissue. The convertibility of collagen into elastin has been suggested, but evidence has not been quite conclusive. In fact, the origin and development of elastin fibers is one of the least known of tissue phenomena. Although chemical observations may be suggestive, certainly structural studies of sections of pure connective tissues of the various age groups revealed no evidence of newly formed fibers or renewal of existent ones which had broken down.

Whether the degeneration or destruction of elastin fibers visible in aged connective tissue is entirely the effect of the time factor of age, that is, a manifestation of tissue catabolism, or whether it is merely the result of decades of wear and tear of unremitting mechanical activity on an elastic structure, is as yet, of course, a matter for speculation or of unwarranted deduction. In the present state of knowledge concerning these apparently acellular fibers, no valid answer to the question is possible. It is a fact that the same effects are seen as often in elderly women as in men of comparable age, and it should be borne in mind that in an urban community, such as that from which the specimens were obtained, women ordinarily do not undertake as heavy physical tasks as their menfolk. These factors would imply that the more or less equal changes seen in their respective elastin fibers are not altogether governed by mechanical stresses. However, this aspect of the subject may be left for future study.

The clinical significance of the relative loss of elastic fibers in the connective tissues of the aged, whether catabolic or mechanical, is obvious. It is quite impossible to damage any part of the musculoskeletal apparatus without traumatizing, to greater or lesser extent, the local connective tissues. At times, in addition to the direct local trauma, more distantly connected elements of the system are involved, as in certain injuries to the vertebral column mentioned previously. In the repair of

these connective tissue areas there occurs a degree of reparative fibrosis, the new fibrous components of which are chiefly, if not entirely, collagen fibers, at the expense of elastic elements. And this occurs in the aged at a time of life when the normal elasticity of the tissue is already decreased by natural causes.

Since the primary object of the present writer's interest in the aging connective tissues was its relationship to post-traumatic recovery of the several parts of the locomotor apparatus, these observations seem to bear rather directly on the management of such states. It has been a matter of experience, for example, that the currently fashionable method of rehabilitation by so-called resistance exercises has, in practice, appeared to be more or less futile in elderly people, and, when practiced in accordance with the techniques and powers customarily described in books and papers dealing with the subject, appears to be a retarding rather than accelerating factor. Since in the elderly one is dealing with a demonstrably less resilient tissue than is present in those age groups within which the method was developed, forcing or urging post-disability restoration of function by the added strain of weights is apt to place undue strains on relatively inelastic periarticular and perimuscular parts. In doing so, one may initiate a vicious cycle of strain-pain-protective spasm which may well result in a state contrary to that for which the method has been prescribed. In actual practice among the elderly this phenomenon is particularly apparent in the shoulder and knee regions. Whether the method employed involves the use of so-called "resistance exercises", or whether the same principle is used in the form of calisthenics in which the body or limb itself is the weighted element, both appear to be equally futile in rehabilitation of the aged. "Light exercise", in the sense of formally designed motions, is a euphemism when used in connection with the aged and is almost invariably ineffective.

This does not mean at all that activity of the affected parts is not to be encouraged in the aged. But it does mean that a natural desire to speed up the recovery of function of an injured part must not lead to over-enthusiastic measures which may prolong, if not reactivate, the strains of a local connective tissue mechanism. It also means that in the management of such trauma in the aged, the natural differences inherent in the connective tissue of the musculoskeletal system must be kept in mind when the choice of method is considered. If ever there was a

medical application for the venerable cliché of "making haste slowly", it may well be the recovery of locomotor function in the post-traumatic locomotor apparatus of the elderly.

In place of the formal exercise for the restoration of function in the post-traumatic locomotor apparatus of the aged person, the encouraged daily increase of purposeful activity has usually produced a more rapid recovery with less discomfort and certainly with more cooperation on the part of the patient. It must be recognized that in an elderly individual, especially after fractures involving the joints or juxta-articular areas such as the common Colles' fracture at the wrist, or malleolar fractures at the ankle, a certain degree of permanent restriction of range of motion is often inevitable. Attempts to overcome this by passive stretching or forced active motion may only reactivate the local inflammatory reaction to strain. The constant encouragement of purposeful activity of a kind customary or congenial to the patient will usually carry recovery to an optimum if not maximum degree of usefulness[14]. Attempts to strive for more often defeat their purpose.

In the aged person, the attainment of an adequate range of painless motion is far preferable to perseverance in attempts to strive for a structurally unobtainable or painful maximum. In the absence of any mechanical block due to skeletal deformity, the lessened resiliency and contractions of the pure connective tissues of the musculoskeletal system are apt to be the principal restraining factors.

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MASSIVE BLEEDING IN DUODENAL ULCER*

WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF THE PRESENCE OF CRATER

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THE subject of upper gastrointestinal hemorrhage has been difficult to analyze because of variable statistics from different centers. Differences in the method of case selection and definition of terms are two of the more important factors involved. This study was undertaken with the view of analyzing one segment of all upper gastrointestinal tract bleeders (duodenal ulcer patients) admitted to a large general hospital. By making our group as uniform as possible, we hope that our data may be more generally applicable. The charts were reviewed retrospectively and special attention was paid to radiographic reports in order to correlate these with the subsequent course of the patient, both inside and outside of the hospital.

Admission to The Mount Sinai Hospital is almost invariably on an ambulatory basis. Occasionally, a private ambulance is employed to transport a patient to the hospital for admission, but there is no ambulance service associated with the hospital.

The patient who has time to go to his private physician with a complaint of tarry stools and is referred to the hospital for admission is far different from the patient who faints after a massive hematemesis and is brought to the hospital by ambulance. The importance of this difference has been stressed by Hinton[1]. Most of our patients fit into the former group although the latter is also well represented.

Definition of terms: In order to fit into the category of massive bleeding in our series, a patient had to have had a recent episode of melena or hematemesis (for one week) and a hemoglobin, during the

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period of hospitalization, of 8 grams per cent or less. Two patients who had a sudden 3 gram drop in hemoglobin and fall in blood pressure were included, although recorded hemoglobin values lay between 8 and 8.5 grams per cent. One of these patients was taken to the operating room almost immediately after this episode.

All of these patients bled from duodenal ulcers, as far as could be determined. All were proven to have duodenal ulcers by x-ray, autopsy report or at operation. No patient who had another lesion, which could have accounted for the bleeding, was included.

These patients were divided into five groups for purposes of analysis, depending on the amount of blood required for stabilization during the admission.

Group	I	0 - 1 unit of blood (500 milliliters each)
Group	II	2 - 4 units of blood
Group	III	5 - 6 units of blood
Group	IV	over 6 units of blood
Group	V	A special group, comprised of the most severe bleeders who either exsanguinated from their disease or who were rushed to surgery for fear of exsanguination.

By definition, all of the medically treated mortalities occurred in this last group (none of whom received less than eight units of blood). (It is realized that the patients in groups I and II would not be considered massive bleeders by some observers[2, 3] because of the ease with which they stabilized, and this will be considered later in calculating the mortality.)

Material Studied

The period of the series under investigation extended from 1947 to 1957 (Table I). There were 1087 patients admitted with a diagnosis of duodenal ulcer; and 352 patients were admitted with a diagnosis of gastric ulcer. Two hundred patients were admitted with a diagnosis of upper gastrointestinal bleeding of unknown etiology. Thirty-five other patients had both gastric and duodenal ulcers. Of the 352 gastric ulcer patients, 51 were admitted because of massive bleeding. These patients are not considered in this paper. Of the 1087 duodenal ulcer patients, 235 were admitted for massive bleeding or bled massively after admission (accounting for 261 admissions). One hundred sixty-one additional

TABLE I—PEPTIC ULCER PATIENTS ADMITTED TO WARD SERVICE THE MOUNT SINAI HOSPITAL JANUARY 1947 TO MAY 1957

Total Duodenal Ulcers	1087
Massively Bleeding Duodenal Ulcers	235 (21.6%)
Total Gastric Ulcers	352
Massively Bleeding Gastric Ulcers	51
Gastric and Duodenal Ulcers	35

duodenal ulcer patients had bleeding as their major complaint, but the amount of bleeding was not great enough to warrant their inclusion in this report. This is an incidence of bleeding in duodenal ulcer admissions of 36.4 per cent (396 of 1087 patients) and an incidence of massive bleeding (as defined above) in duodenal ulcer admissions of 21.6 per cent.

The Mount Sinai Hospital has, up to now, been oriented toward the medical aspects of cure for these patients. This accounts for the fact that 204 of the 235 patients were admitted to the medical services (224 of 261 admissions). Surgery, when performed, was rarely done during the first 72 hours of hospitalization. When it was performed during the bleeding admission, it was usually done after all evidences of bleeding had subsided. Some of the patients who had surgery performed on re-admission were bleeding actively.

AGE AND SEX

The age and sex distribution in this series is noted in the accompanying charts (Tables II and III) and was found to be similar to that reported in other series[4, 5]. One hundred seventy-four patients were over 40 years of age. This represents the group of patients that can withstand prolonged anemia or tissue hypoxia the least well and therefore accounts for the major portion of the mortality figures[4, 6]. The age distribution was similar among the different bleeding groups and suggests that the older patient is *not* more apt to have a massive hemorrhage than a less severe bleeding episode.

The greater incidence of bleeding in male patients can be noted in the charts. Over-all, the ratio of males to females was a little over 2:1. It ranged from 1.5:1 and 2:1 in groups I and II respectively, to roughly 3.5:1 in groups III, IV and V.

TABLE II—AGE DISTRIBUTION OF PATIENTS PER BLEEDING GROUP

GROUP	1-20 years	21-39 years	40-59 years	60 years or over
I	0	10	13	6
II	4	27	51	42
III	1	11	13	14
IV	0	4	15	6
V	1	3	5	9
Totals	6	55	97	77

TABLE III—SEX DISTRIBUTION OF PATIENTS PER BLEEDING GROUP

Group	*Males*	*Females*
I	17	12
II	80	44
III	31	8
IV	20	5
V	13	5
Totals	161	74

The better prognosis in females with this disease has been noted frequently before[7, 8] and, while of interest, has not been adequately explained, and is difficult to apply in the individual case.

SYMPTOMS

Melena was, by far, the most common symptom, followed by hematemesis, signs of weakness, vertigo or fainting, and epigastric pain. Hematemesis occurred in 19 per cent of group I patients and in 28, 42, 35, and 50 per cent of groups II, III, IV and V respectively. Melena was remarkably constant, occurring in about 85 per cent of patients in each group. Pain was present in about 19 per cent of each group, with little change in incidence among the groups. Signs of weakness or fainting occurred in roughly 40 per cent of patients in each group. In the less severe bleeders this was manifested as mild weakness or light-headedness, and in the more severe bleeders, syncope or collapse was prominent. As mentioned elsewhere, hematemesis and collapse remain the most impor-

TABLE IV—DURATION OF PREVIOUS ULCER SYMPTOMATOLOGY IN RELATION TO BLEEDING GROUPS

Group	*None*	*Less Than 1 Year*	*1-4 Years*	*5-9 Years*	*10 or More Years*
I	5	3	9	4	10
II	24	8	38	32	38
III	11	3	9	5	15
IV	7	0	8	5	9
V	6	1	4	2	5
Total	53	15	68	48	77

TABLE V—NUMBER OF PREVIOUS BLEEDING EPISODES IN RELATION TO BLEEDING GROUPS

Group	*None*	*1*	*2*	*3*	*More than 3*
I	15	12	1	2	1
II	73	35	16	7	7
III	27	9	3	1	3
IV	14	8	5	1	1
V	13	0	4	0	1
Total	144	64	29	11	13

tant symptoms which may indicate the severity of a particular bleeding episode[2, 8, 9].

An analysis of the duration of previous symptoms and number of previous bleeding episodes with relation to severity of bleeding was made. No attempt to divide these ulcers into acute and chronic was made, as has been done in the past, especially in the British literature[6, 8]. The data are summarized in Tables IV and V. It is significant that from 53 of the 235 patients no history of previous symptomatology could be elicited. Thirteen of 47 patients in groups IV and V had no previous symptomatology. Seventy-seven patients had symptoms of ulcer for over ten years.

For the majority of patients, this was the first bleeding episode of any kind (144 patients). Twenty-seven of 47 patients in groups IV and V were in this category.

Treatment

Only medical treatment was given to 188 of the original 235 patients. Forty-seven patients underwent surgery during the original admission and an additional 47 patients underwent surgery at the time of readmission to the hospital. The indication for surgery was bleeding (either multiple episodes, recurrent, or uncontrollable massive) in almost every instance.

Mortality and Morbid Anatomy

Of the 188 patients treated only by medical means, seven patients died, a mortality rate of 3.7 per cent. These patients were transfused 8 to 33 times. All seven patients were over 56 years of age, six were males and one was female.

Of the 47 patients undergoing surgery at the first admission, three died, a mortality rate of 6.4 per cent. Of these three patients, one was a child of six years who was subjected to an exploratory laparotomy for bleeding, but the site of the lesion could not be located. He continued to bleed postoperatively and expired. At postmortem examination, an acute ulcer of the duodenum was found to have eroded into the superior pancreaticoduodenal artery.

Another patient was a 54 year old female, who had an emergency subtotal gastric resection performed, but the base of the ulcer was left *in situ*. She continued to bleed postoperatively and expired. Permission for postmortem examination was not obtained.

The third surgical fatality occurred in a man, age 57, who had a Billroth I subtotal resection plus vagotomy performed because of continuous slow bleeding, with persistent melena during 27 days of hospitalization on the medical service. He suffered a cardiac arrest on the operating table, from which he recovered, only to die on the 17th postoperative day with evidence of cerebral hypoxia. His hemoglobin hovered around 8 grams per cent during his first 25 days in the hospital, and it was not until the day prior to operation that two units of blood were administered. Possible errors in judgment are probably associated with all of these deaths.

Pathologic findings are available in five of the seven deaths which followed only medical treatment and in all of those deaths following surgery. In all of the specimens obtained the ulcer was located on the posterior duodenal wall, penetrating into the pancreas. Erosion of the

TABLE VI—SURGICAL MORTALITY

A. PATIENTS UNDERGOING SURGERY WHILE ACTIVELY BLEEDING

Operation	*Number of Patients*	*Mortality*
Billroth II	14	1
Billroth II and Vagotomy	3	0
Gastroenterostomy	0	0
G.E. and Vagotomy	4	2
Billroth I	2	1
Exploratory Laparotomy	1	1
Total	24	5 (20.8%)

B. PATIENTS UNDERGOING ELECTIVE SURGERY (BLEEDING SUBSIDED)

Operation	*Number of Patients*	*Mortality*
Billroth II	28	0
Billroth II and Vagotomy	29	1
Gastroenterostomy	2	0
G.E. and Vagotomy	11	0
Total	70	1 (1.4%)

superior pancreaticoduodenal artery or one of its branches was present in five. Of the 18 patients in group V, pathologic details are available in 14. In all of these the ulcer was located on the posterior duodenal wall.

Of the 47 patients who underwent surgery at the time of readmission to the hospital, an additional three patients died. The over-all surgical mortality with bleeding as an indication for operation (but not necessarily all massive bleeding) was, therefore, 6.4 per cent. Information was obtained to determine which of these patients were bleeding actively at the time of surgery, as evidenced by melena, hematemesis, or a falling hemoglobin. Twenty-four of the 94 patients operated upon were in this category and five of the six deaths occurred among these patients (20.8 per cent). Of the truly elective procedures (bleeding subsided), there was one death among seventy patients (1.4 per cent, Table VI). Of these five deaths in the actively bleeding, surgically treated patients, four were operated upon 4 to 33 days after admission (one patient receiving 34 units of blood preoperatively). The remain-

ing patient was the woman mentioned earlier who had the base of the ulcer left in place at the time of surgery. It is interesting to note that of the five deaths occurring in the actively bleeding group, two occurred in patients who had had a vagotomy and gastroenterostomy done as the primary procedure. We do not, at this time, recommend this operation alone in the treatment of active bleeding. It is our belief that, if this operation does have a place in the treatment of bleeding ulcer, it must be accompanied by ligation of the bleeding point in the ulcer. The over-all mortality of both medically and surgically treated patients was 4.3 per cent in our series.

According to some, the classification of massive and non-massive bleeders should be based upon the amount of blood replacement required by the patient, with 2000 milliliters as the dividing line[10]; those requiring more than this amount are classified as massive bleeders. We agree that our groups I and II are highly favorable cases for any type of treatment, since these patients stabilize quickly or cease to bleed soon after admission. In order not to weight our mortality figures with this type of bleeder, we recalculated our mortality on the basis of the last three groups alone (over 4 units of blood). This is significant because, with each unit of blood transfused, new probabilities arise as to the survival of the patient. One must keep constantly in mind the changing percentages in favor of and against the patient as his course in the hospital progresses.

Of 82 patients in groups III, IV and V, nine died. This is an over-all mortality of 11 per cent. Of 24 patients in the above groups receiving surgical treatment during their original admission, two died (8.3 per cent). Of 58 patients in the above groups who were treated only by medical means, seven died (12.1 per cent).

Follow-Up Investigation

Twenty-four of the patients in our series were readmitted to the hospital with massive upper gastrointestinal tract bleeding, accounting for twenty-six readmissions. All of these patients had originally received only medical treatment. This represents an absolute minimal failure rate of medical treatment of 12.8 per cent in our hands. These are patients whose lives were in jeopardy twice from their disease.

Follow-up data are summarized in Tables VII, VIII, and IX. Of 188 patients treated medically in our series, 104 were followed for a

TABLE VII—SUMMARY, MEDICALLY TREATED PATIENTS

Number of Patients Treated Medically	188 (80%)
Mortality	7 (3.7%)
Number of Patients Followed More Than One Year	104 (57.5%)
Average Length Follow-Up	5.1 years
Bled Again After Discharge	53 (50.9%)
Operated Upon Subsequently	40 (38.5%)

TABLE VIII—SUMMARY, SURGICALLY TREATED PATIENTS

Number of Patients Treated Surgically	47 (20%)
Mortality	3 (6.4%)
Number of Patients Followed More Than One Year	28 (63.6%)
Average Length of Follow Up	4.7 years
Bled Again After Surgery	3 (10.7%)

period of over one year (average 5.1 years). This is a 57.5 per cent follow up, excluding the seven who died while in the hospital. Of these 104 patients, 53 bled again after discharge (50.9 per cent), and 40 (38.5 per cent) came to elective surgery or were operated upon during a period of recurrent bleeding. (Patients who were operated upon or who bled, but whose total follow-up was for less than one year, are excluded from these calculations.)

Of the original 47 surgically treated patients, 28 (63.6 per cent) were followed for over one year (average 4.7 years) and 3 (10.7 per cent) had recurrent bleeding after discharge. In order to evaluate more fully surgical therapy for this disease, we included in follow-up an additional 31 patients who had subsequent surgery (part of the group originally treated medically). This brings our follow-up to 59 of 94 patients (67 per cent) treated surgically for bleeding duodenal ulcer, and of these, 11 patients bled again (18.6 per cent).

RADIOLOGICAL FINDINGS

A special aspect of this problem was that which concerned the roentgenographic findings in these patients during their stay in the hospital. At this hospital, x-ray examination of the gastrointestinal tract

TABLE IX—SUMMARY OF SURGICALLY TREATED PATIENTS PER OPERATION TYPE

(INCLUDING THOSE ORIGINALLY TREATED MEDICALLY AND REQUIRING SUBSEQUENT SURGERY)

Operation	*Number of Patients*	*Mortality*	*Number Followed More Than 1 Year*	*Number Who Bled After Surg.*
Billroth II	42	1 (2.4%)	25 (60.9%)	5 (20%)
Billroth II and Vagotomy	32	1 (3.1%)	25 (78.1%)	2 (8%)
Gastroenterostomy	2	0	2 (100%)	1 (50%)
G.E. and Vagotomy	15	2 (13.3%)	7 (53.8%)	3 (43%)
Billroth I	2	1 (50%)	0	—
Exploratory Laparotomy	1	1 (100%)	0	—
Totals	94	6 (6.4%)	59 (67.0%)	11 (18.6%)

has rarely been performed in the past during the stage of active bleeding. Except for the three patients in group V who had their x-rays taken before massive bleeding became apparent, the examinations were carried out when the patients were stable and usually having guaiac-negative stools. The findings were divided into two groups: those with craters and those without.

SIGNIFICANCE OF CRATER

To the radiologist, the crater is defined as the persistent presence of a localized, rounded collection of barium[11]. According to Berg[12], the deep crater and rolled up margin of a callous ulcer are easy to demonstrate, but in ulcers confined to the superficial mucosa, the crater may be so shallow that it is quite impossible to demonstrate it roentgenologically in the living subject. The presence of a crater on x-ray indicates that the ulcer has penetrated into submucosa or muscle[13].

In our series, remarks in the x-ray reports as to the presence of a persistent patch or fleck of barium in the bulb were considered as evidence of crater. If only radiation of folds was mentioned, it was considered part of the no-crater (deformity only) group. The facts that came to light during this investigation are summarized in Tables X and XI.

Crater was a more constant finding in the more severe bleeding

TABLE X—CRATERS IN ROENTGENOGRAMS IN BLEEDING GROUPS

Group	*With Craters*	*Without Craters*	*Incidence*
I	8	20	28.6%
II	35	86	28.9%
III	17	23	42.5%
IV	13	6	68.4%
V	3	0	100%

TABLE XI—COMPARISON OF ROENTGENOLOGIC FINDINGS IN PATIENTS TREATED MEDICALLY (WHO HAD X-RAYS) AND FOLLOWED AT LEAST ONE YEAR OR UNTIL RECURRENT BLEEDING OR SURGERY

Findings	*No. of Patients Treated Medically*	*No. of Patients Followed*	*No. of Patients with Recurrent Bleeding*	*No. of Patients Undergoing Surgery*
Crater	65	40	29 *(72.5%)*	24 *(60%)*
No Crater	119	75	30 *(40%)*	20 *(26.7%)*
Total	184	115 *(62.5%)*	59 *(51.3%)*	44 *(38.3%)*

groups, being present in 28.6, 28.9, 42.5, 68.4 and 100 per cent of patients who had x-rays in groups I through V respectively. It was also noted that there was a difference in the prognosis, with respect to recurrent bleeding and subsequent surgery, among medically treated patients, depending on whether or not craters were demonstrated during hospitalization for bleeding. Of those medically treated and not showing craters (119 patients) 40 per cent bled again and 26.7 per cent of those followed required subsequent surgery. Of those medically treated and showing craters (65 patients) 72.5 per cent bled again and 60 per cent of those followed required subsequent surgery (difference significant p equals .001).

DISCUSSION

A group of 100 massive bleeders reported from one institution may bear little resemblance to a group of a hundred massive bleeders reported from another hospital. We should determine the number of different types of bleeders in each series, for the mortality will vary in

each type. We should be aware of the criteria for the selection of patients that are inherently involved with the different sources of patient material in various centers. The definition of the term "massive bleeder" used by authors, as well as the methods by which the diagnosis is confirmed, is of great importance to the proper analysis of the statistics. Hemoglobin levels are sufficient only if the subsequent course of the patient is taken into consideration. For example, Finsterer[14] showed that if hemoglobin levels dropped to 40 per cent or below, and red blood cell count to 2.5 million or below, the mortality increased from 2-5 per cent to 11-25 per cent. In our series, the difference in definition of the term "massive bleeder" accounted for a change in mortality of medically treated patients from 3.7 per cent to 12.1 per cent.

In the bleeding duodenal ulcer group taken as a whole, medical treatment is the preferred method of immediate management. We should distinguish, after 24 to 48 hours of medical therapy, a separate group of these patients who still require transfusion after having received 2000 milliliters of blood. The mortality in this latter group will be less with early surgical treatment than with continued medical treatment alone. Exception may be made in those patients under 45 years of age, where an additional 24 hours' observation may be allowed, but patients who require 2000 milliliters of blood in less than 24 hours should be candidates for immediate surgery. If, after 48 hours, the patient is still bleeding, as evidenced by fresh blood via the Levine tube, a continued fall in hemoglobin or recurrent hematemesis, then the patient should be taken directly to the operating theater. Should he recover on medical treatment, he has a 50 per cent chance of bleeding again, and a 12 per cent chance of bleeding massively again (our figures). On the other hand, should surgery become necessary after this critical period of active bleeding or during active bleeding on a subsequent admission to the hospital, then the mortality becomes very high.

The figures quoted in other series are not dissimilar from those found by us. Heuer[15] reported a 29 per cent mortality in patients undergoing surgery while actively bleeding as opposed to 4 per cent in those undergoing elective surgery. He mentions a 10 per cent mortality in those undergoing early surgery as opposed to 70 per cent in those undergoing late surgery. Fraser and West[16] found a 33.3 per cent mortality in late surgery for actively bleeding duodenal ulcer. The figures often quoted from Finsterer[14] are 33.3 per cent for late operation as against

5.1 per cent for early operative intervention.

Previous attempts to compare surgical and medical mortality rates have been grossly biased by the failure to realize that the surgical figures used were those based on the results of late surgery. Patients operated upon under these conditions were operated upon after a trial of medical therapy had failed. For a proper comparison, only the results of early surgery should be compared with medical treatment at the same institution. (This would also tend to control such variables as selection of cases and definition of terms.) Stewart[17] reported on 65 cases of surgically treated peptic ulcer (including gastric ulcer) with massive bleeding, with a mortality of 10.7 per cent, only five of whom were operated on later.

This is in contrast to 42 medically treated patients with a 21.4 per cent mortality. (Our mortality figures are lower because we excluded all gastric ulcers.) Jones[6] has stated that whereas he formerly treated all these patients almost solely by medical means, he now maintains a sharp surgical bias, with respect to emergency surgery. Concomitant disease in the older age groups is an indication for earlier surgery, not a contraindication. These patients cannot tolerate the effects of tissue hypoxia due to prolonged anemia[9, 17, 18].

If the immediate salvage of the patient is the only consideration in his treatment, then follow-up statistics have nothing more than academic interest. It is true that the majority of patients who bleed massively do not bleed massively again[7], although the occurrence of minor bleeding episodes is frequent[3, 19]. However, how can one consider a particular plan of management successful just because the patient leaves the hospital alive, if he is to return once again, a victim of the ravages of his disease? In addition, who can estimate the price of recurrent melena with concomitant anemia that must be paid for by the tissues of the body? Statistics to evaluate this factor are not as yet available.

The burden of improving the prognosis in these patients lies heavily on the shoulders of the surgeon. Hasty surgery is not the answer. Treatment of the bleeding point alone is not the answer. One must keep in mind the significance of the "ulcer diathesis" in these patients. Subtotal gastric resection is the best method of dealing surgically with this problem that we have at hand at this time[20]. Ligation of the involved vessel should be accomplished whenever possible. The incidence of recurrent bleeding after surgical treatment in our series agrees with that found by

Jordan[3], although our figures for medically treated patients disagree. (Other series report the incidence of recurrent bleeding after medical treatment as high as 70 per cent[2].)

The large number of previously asymptomatic patients in our series is one of the strongest arguments in favor of early x-ray examination. Certain observations are common in treating these patients. They rarely bleed steadily to exsanguination. The course of the bleeding usually has peaks and valleys during which the patient may appear to stabilize before having another episode of massive hematemesis. Opportunities for these early examinations are present. Careful studies of pathologic material, reported elsewhere, have demonstrated the reason for these observations. Thrombi have been demonstrated in the eroded vessels at the bases of bleeding ulcers[9, 18, 21, 22]. The significance of this is that these people do maintain their hemostatic mechanisms. It is the re-erosion of these thrombosed vessels that produces the intermittent bleeding. In our present state of knowledge, we must assume that it is the acid peptic factor that is involved and it is with this that we must deal.

Incidentally, there is little evidence to support the contention that arteriosclerosis of the involved vessels occurs in older patients, preventing retraction. Material studied indicates that necrosis of the arterial wall occurs during acute erosion, breaking up the elastic fibrils and thus preventing retraction[22]. The increased mortality of this disease in the older age groups need not be explained on the basis of local vascular factors, but can be explained on the basis of more generalized bodily changes.

The posterior wall ulcer is not the only one that bleeds. Ulcers in other locations may bleed enough for the patient to be classified as a massive bleeder. However, the ulcer in which bleeding becomes a hazard to the life of the patient will almost always be located on the posterior duodenal wall[9], usually penetrating into the pancreas, and often eroding a large artery[15]. The significance of persistent pain as a bad prognostic sign, as noted frequently by Jones[6, 8], is, we believe, related to this phenomenon. Anything which will give us a clue to the location of such an ulcer early in its course would be of great value in the management of the patient.

As mentioned earlier, the emergency roentgenologic examination is of value in establishing or confirming the diagnosis. If the patient is not in severe shock or actively vomiting, this can be done safely and effec-

tively[10, 23-26]. We know that duodenal ulcer can be diagnosed on x-rays taken during active bleeding[26, 27]. We know that craters can be demonstrated without palpation or compression[25, 27]. There is no good evidence in favor of the view that x-ray examination increases the chance of recurrent bleeding. (We have recently gone so far as to empty a stomach filled with clotted blood by means of an Ewald tube, in order to get confirmation of the lesion by roentgenologic techniques.)

The presence of an ulcer crater on x-ray does not preclude its presence on the posterior wall and, in that sense, make it more likely to bleed massively. However, we have found a significant difference in prognosis in our series, depending on whether or not a crater was demonstrated on x-ray. The presence of a late crater is evidence that the patient has had a protracted course, as seen by the increasing frequency of their appearance in the more severely bleeding patient. From our present data we cannot draw any conclusions as to the diagnostic value of craters which appear early in the course of a bleeding episode or which appeared on a previous admission. The size and location of the ulcer crater may also be important. These aspects of the problems need to be investigated further.

Craters have been known to disappear on medical therapy for duodenal ulcer[27], including those that have been bleeding. However, the presence of a crater late in the course of a medically treated bleeding duodenal ulcer patient indicates, we believe, some intractability of the disease, and would tend to make us lean more toward surgical therapy for this ulcer before the patient is discharged. (Almost three out of four of these patients will bleed again and over half will require operation later, in any case!)

It is, therefore, suggested that a patient showing a crater on emergency gastrointestinal x-ray series during bleeding will have a longer and more protracted course, and poorer prognosis for cure than one showing only a deformity of the bulb. If this proves to be a valid assumption, then another tool is at hand to aid us in the management of these patients.

Summary and Conclusions

1. An analysis was undertaken of 235 patients with massively bleeding duodenal ulcers admitted to the wards of The Mount Sinai Hospital from 1947 to 1957.

2. The patients were divided into four bleeding groups on the basis of the number of units of blood they required to become stabilized. The fifth group was made up of patients who became exsanguinated while on medical therapy or who were taken to the operating room for emergency surgery.

3. The mortality rate for the 188 medically treated patients was 3.7 per cent. The mortality rate for the 47 surgically treated patients was 6.4 per cent.

4. The mortality rate of an additional 47 surgically treated patients who bled after discharge or were operated upon electively was 6.4 per cent.

5. The surgical mortality rate during active bleeding was 20.8 per cent in contrast to 1.4 per cent for entirely elective procedures.

6. The mortality rate in those treated medically in the last three groups (those requiring more than 2000 milliliters of blood) was 12.1 per cent. The mortality rate in those treated by surgery in these same groups was 8.3 per cent.

7. Follow-up of 104 medically treated patients revealed a 50.9 per cent incidence of recurrent bleeding compared to an 18.6 per cent incidence in all surgically treated patients.

8. Billroth II subtotal gastric resection plus vagotomy yielded the lowest incidence of recurrent bleeding (8 per cent).

9. A review of roentgenographic findings in these patients revealed a higher incidence of the presence of crater in the more severely bleeding groups.

10. Follow-up of patients treated medically revealed that when no crater was demonstrated during the hospitalization for the bleeding episode, the incidence of recurrent bleeding was 40 per cent. When a crater was demonstrated during hospitalization, bleeding recurred in 72.5 per cent of the patients.

11. Follow-up of medically treated patients revealed an incidence of subsequent surgery of 26.7 per cent if no crater was demonstrated, and 60 per cent if a crater was shown to be present.

12. It is recommended that patients with acute massive hemorrhage of duodenal ulcer origin be operated upon much sooner when a crater is demonstrated roentgenologically.

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BLOOD PROTEINS

*Transcription of a Panel Meeting**

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* Presented at the Postgraduate Week on *Research Contributions to Clinical Practice*, at The New York Academy of Medicine, October 11, 1957.

MODERATOR HENRY G. KUNKEL: In line with the theme of the Postgraduate Week, today's panel discussion is on recent developments in the field of blood proteins. Before beginning, I think we ought to clarify the title. The discussion will be limited to serum and plasma proteins and not include the broad field of hemoglobins and other red cell proteins. We would like very much to have this meeting as informal as possible and have frequent questions and answers among the panelists. I know that some of our panelists have disagreed in print and I hope they will continue to disagree here. Perhaps they might even settle some of their differences.

One of the subjects that the committee was particularly anxious for us to cover today is that of zone electrophoresis and its clinical usefulness. I should like to have Dr. Elliott F. Osserman start us off. He has had a wide experience in this field, particularly relating to his large collection of myeloma patients. Dr. Osserman!

DR. ELLIOTT F. OSSERMAN: I think most of you are aware of the fact that in the past seven years, since 1950, the technique of filter paper electrophoresis has been made available in a large number of clinics and hospital laboratories as well as research laboratories. Electrophoresis itself is a technique which is approximately 20 years old, but prior to the development of the filter paper modification of this basic technique of electrical separation of charged protein molecules, electrophoresis was a cumbersome, expensive and a time-consuming procedure. With the development of the filter paper modification, most of the expensive equipment could be dispensed with and a separation of serum proteins could be carried out with a small expenditure of time and equipment.

Our use of this technique began in 1951. In the past six years we have employed a filter paper system as the routine technique for serum protein determinations at the Francis Delafield Hospital, and more recently, paper electrophoresis has been made a routine procedure at the Presbyterian Hospital.

In general, it has been found that the amount of clinically useful information that can be derived from a filter paper electrophoretic pattern far exceeds that which can be obtained from a determination of "A/G", the albumin and globulin, by either a salt or alcohol precipitation technique.

(Slide) Shown in the slide is a group of serum protein patterns in a variety of clinical states. This slide was loaned to me by Dr. Kunkel

and actually belongs to Dr. Laurell of Sweden. Dr. Laurell spent some time with Dr. Kunkel at the Rockefeller Institute, and on his return to Sweden he graciously left some of his slides with Dr. Kunkel. The anode is to the left; the cathode to the right. Dr. Laurell has recently described a modification of the technique whereby the addition of calcium ions to the standard veronal buffer solution provides a separation of beta globulin into two constituents, beta-1 and beta-2. From this slide, the important point to be noted is that the majority of changes in which we, as clinicians, are interested are *qualitative* rather than *quantitative* changes. When a serum protein partition is requested for diagnostic purposes, one is usually attempting either to differentiate the cause of a hyperglobulinemia, document a nephrotic syndrome, or rule in or out agammaglobulinemia as the cause of recurrent infections. In great measure, the information being sought is apparent by simple examination of the original pattern, and does not require expensive photometric or elution quantitation. For example, in cirrhosis, the gamma globulin is *diffusely* increased, and albumin is decreased. The alpha globulins are not particularly changed. The alpha-2 may be slightly elevated but alpha-1 globulin is usually within normal limits. In systemic lupus erythematosus, as in the other so-called collagen diseases, one again observes a diffuse increase in gamma globulin but, as well demonstrated here, the lupus globulin increase is not quite as diffuse as that observed in cirrhosis; it is relatively more homogeneous than the cirrhotic gamma. In multiple myeloma, the major change consists in the appearance in the serum of an abnormal protein which is electrophoretically homogeneous. In this set of patterns, the myeloma serum shows a distinct band in the fast-gamma range, but this band may migrate anywhere in the gamma or beta globulin ranges. Interestingly, and of some clinical significance, is the *decrease* in *normal* gamma globulin which is evident in the myeloma pattern. The serum pattern in macroglobulinemia is indistinguishable from the myeloma abnormality. Macroglobulinemia is considered to be a syndrome related in its pathogenesis to myeloma. The diagnosis of macroglobulinemia cannot be made solely from the electrophoretic findings, but requires the ultracentrifugal determination of the sedimentation constant of the abnormal protein to ascertain that a large molecular weight constituent is present.

The point I wish to stress is that a precise quantitation of individual

serum protein constituents is not needed for the majority of clinical diagnostic purposes. More significant than precise quantitative changes are the qualitative changes. In this regard, clinical electrophoresis resembles clinical electrocardiography.

(Slide) The next slide shows a picture of a very simple filter paper electrophoresis system which we have employed in our laboratories at the Delafield Hospital. This apparatus can be put together for less than $100. Examples of the patterns that are obtained with this system are shown on the next slide. The serum samples are applied as spots to the paper, resulting, after separation, in a series of rounded spots, as opposed to the previously seen bands. Despite the differences in technique, though, the major types of changes are again evident. We observe a diffuse increase in gamma globulin in cirrhosis, as opposed to the discrete abnormal component in myeloma. Seen also is the characteristic pattern in the nephrotic syndrome—a very marked decrease in albumin, an abnormal constituent in the alpha-2 and beta region consisting of lipoprotein and glycoprotein, and a decrease in gamma globulin.

Regarding all serum protein separation procedures, including electrophoresis, ultracentrifugation, Cohn fractionation, etc., we must recognize that there are many hundreds of different serum protein constituents and no single method will delineate and quantitate all of these fractions. An albumin-globulin separation, such as the Howe technique, provides a partition of two large and heterogeneous constituents; electrophoresis permits separation of five or six components. To this extent electrophoresis can be expected to provide a greater amount of clinically useful information, but as Professor Wuhrmann of Zurich has suggested, an electrophoretic pattern is comparable to a silhouette of the Swiss Alps. The major elevations are broadly outlined, but the constituent slopes and crags are not delineated.

MODERATOR KUNKEL: Thank you, Dr. Osserman.

Is there any discussion from the opposite point of view, that perhaps filter paper electrophoresis is being used too much in hospitals at the present time? Dr. Bearn!

DR. A. G. BEARN: Dr. Osserman has given a very elegant discussion of some of the advantages of paper electrophoresis over the albumin-globulin ratios. But I was thinking, as he spoke, that the conditions in which paper electrophoresis are diagnostically valuable, by and large,

are rather uncommon. Multiple myeloma is not really a very common disease, and I wondered whether the performance of flocculation tests might not be almost as valuable as a rapid screening technique. In short, I wonder whether some conservative middle path could be adopted so that perhaps a combination of flocculation tests and the paper electrophoresis in hospitals might not have some advantage over the carrying out of paper electrophoresis routinely. I think it might be argued that routine paper electrophoresis may be rather wasteful and in the hands of non-experts actually misleading, and so I wonder whether perhaps it might be better to reserve it for those cases in which there was some other indication of abnormal protein metabolism, say an abnormal flocculation test.

MODERATOR KUNKEL: *Do you have any discussion on this point?*

DR. OSSERMAN: Our experience suggests that electrophoresis is not being utilized enough, Dr. Bearn! We have been particularly impressed by the marked serum protein abnormalities seen electrophoretically in the general clinic and ward populations under care in the Presbyterian Hospital. This group of patients is probably less profoundly ill than the Delafield group. There are many more patients with degenerative vascular disease, infections, diabetes, etc., as opposed to advanced neoplastic states, and yet, among these general hospital patients we are observing a remarkable number with major quantitative changes in albumin and alpha globulins which may well be of clinical significance.

MODERATOR KUNKEL: *Don't you think that there might be some danger in proposing this as a general clinical technique? I was wondering about the pitfalls in advocating a sort of dermatological approach to reading these patterns,—how much trouble eventually this might lead to, with people who would use this approach and are not well trained in it.*

DR. OSSERMAN: As mentioned before, some of the problems presented by paper electrophoresis may be comparable to the problems with electrocardiograms. At times, the changes observed are major ones which require little skill or experience to recognize. At other times, the changes are more subtle. In these instances, the laboratory tool is only as good as the individual interpreting the results. Again, like the electrocardiogram, a serum electrophoretic pattern should be interpreted in the light of the clinical and then of the laboratory features

presented by the patient.

MODERATOR KUNKEL: *There have been some rumors about some fantastic development in gel electrophoresis and many people have wondered whether this is going to replace the present paper methods. Dr. Bearn, you have had some experience with this method.*

DR. BEARN: We have recently become interested in the method of starch gel electrophoresis. It was originally developed by Dr. Oliver Smithies of Toronto and has been used at Cornell Medical College by Dr. James Pert and Dr. Ralph Engle.

The method depends upon the fact that if you heat partially hydrolyzed starch with borate buffer and then pour it, while still hot, into a suitable container it will solidify in the form of a firm gel. Rather curiously, it is now possible to perform electrophoresis in this solid medium. The sample of serum can be inserted into the gel either by means of filter paper or in a slurry with starch grains. This technique would not have any clear advantage if by this means one only got the normal number of electrophoretic bands but, in fact, with electrophoresis in a starch gel, the serum proteins split up into many more components than are seen under conditions usually employed in paper electrophoresis. The reason for this is certainly to some extent obscure but it depends in part upon the fact that although proteins may share the same electrical charge they may differ in size. The gel can act as a kind of sieve, and thus may be able to separate proteins which, although they have a similar electrical charge, differ slightly in size or shape.

(Slide) This slide represents the starch gel pattern which has been obtained on alpha-2 proteins isolated from normal serum. Normal alpha-2 protein was first separated by starch block electrophoresis, eluted, concentrated, and re-run in a starch gel. You can, I think, see at least eight separate bands. The slowest migratory band is the heavy component of the alpha-2 which we know to have an s rate of 19. This protein has more difficulty in getting through the gel, so it migrates more slowly than the rest of the alpha-2 proteins. This method will require a greater degree of development before it can be advocated as a clinical tool.

DR. I. HERBERT SCHEINBERG: Is this re-run carried out under the same conditions of ionic strength and pH as the original run?

DR. BEARN: It certainly is not. It is a good point. A great deal of

this improved separation may well depend upon the fact that the electrophoresis is carried out at a low ionic strength. I don't think we really know why these protein bands are separating so well and of course it would be presumptuous for us to assume that any of these bands, be they ever so narrow, represent single proteins.

DR. MORRIS ZIFF: How about the gel? Do different preparations of the gel have different pore size and produce different patterns?

DR. BEARN: It would be nice to make a whole series of gels of varying pore size. Unfortunately, one of the problems seems to be that the method is rather empirical, and thus far it has not been possible to make a tailor-made gel of precisely known pore size.

DR. ZIFF: Suppose the gel runs out, can you reproduce the pattern the next time you make a new gel?

DR. BEARN: That is an important question. If you use the same starch and use identical conditions, I think the patterns are very reproducible; but it does require care.

MODERATOR KUNKEL: *Can you scan these gels?*

DR. BEARN: Yes, this has been done. Dr. Pert has had some success with this technique. One can also cut these gels up and, after freezing and thawing, extract the protein. From the point of view of recovery of all the proteins applied there is still a problem.

DR. OSSERMAN: Has anything been seen in the starch gel patterns of whole serum that is possibly of any clinical usefulness? I heard some report about the peculiar band in acute leukemia, I believe from Dr. Pert's group.

DR. BEARN: I have not heard that. It is certainly interesting if it is so.

DR. ZIFF: Is there anything to the idea that there are genetic patterns in serum by this technique?

DR. BEARN: Yes, there are.

MODERATOR KUNKEL: *To continue on methodology: Dr. Scheinberg was formerly with the Harvard group under Dr. Cohn, working on plasma fractionation, and perhaps he can tell us a little about this method. I have often wondered why it has not had broader clinical application.*

DR. SCHEINBERG: I think it is because paper electrophoresis has become a happy medium: less work than fractionation, more information than the A/G ratio. I wonder whether the method which Dr. Ziff is going to tell us about, cellulose ion exchange chromatography, is not the best of all, yielding maximum information most feasibly.

Fractionation means breaking plasma down into its protein components and can be either analytical or preparative. Essentially, free, paper and starch electrophoresis are analytic fractionating tools. One wants to see how plasma from a patient with one disease differs from plasma from a patient with another disease. Of course electrophoresis can also be used for preparation. For example, Dr. Bearn pointed out that you can fractionate alpha globulin from serum by electrophoresis. This and the other methods of fractionation for preparative purposes permit the physician to get hold of gamma globulin, albumin, fibrinogen or whatever fraction he may need for his purposes.

Before discussing Dr. Cohn's methods in some detail it might be well to recall that there are a number of ways of fractionating proteins. One can do it by electrophoresis, as we have just seen. One can use a gravitational field obtaining ultracentrifugally fractionated proteins. Usually ultracentrifugation is analytical, but it can be preparative. So far as I know nobody has ever separated proteins in a magnetic field but it is the kind of thing that Dr. Kunkel might do next year. For over half a century, people have fractionated proteins by varying salt concentrations, as in Howe fractionation. The latter depends upon an arbitrary splitting into two fractions, "albumin" (A) and "globulin" (G), one of which is soluble and one of which is not, in a certain concentration of a sulfate salt. And, as we shall hear from Dr. Ziff, fractionation can be carried out chromatographically.

Dr. Cohn, starting back in the middle 1920's, decided that plasma proteins could be fractionated preparatively. He devised a system which utilized five variables: the temperature; the concentration of an organic substance, which in his case was ethyl alcohol; the ionic strength, essentially the concentration of the salts in the solution; the concentration of the protein itself, which could be varied by adding water or drying; and pH, or the concentration of hydrogen ions. By varying these and juggling them about in a fairly complicated procedure, he was able to fractionate a great many proteins from plasma. In a moment I should like to show two slides that describe some of the advantages and results of this fractionating system.

Just before Dr. Cohn died, four years ago, he had become dissatisfied with this procedure because he was sure that the addition of alcohol and the variation of pH denatured many proteins. So with his co-workers in Cambridge, Drs. Oncley, Surgenor and several others,

he began to develop a method of fractionating plasma in which the pH is kept essentially at the pH of blood, no alcohol is added, the temperature is kept at zero throughout the fractionation and advantage is taken of the fact that certain metals, such as zinc, can precipitate proteins rather specifically. This new method of fractionation has not yet replaced the old five variable method, and albumin, fibrinogen and gamma globulin are usually prepared by some modification of the old method. I mention the new method only because I think it will eventually result in the isolation of many proteins in a state more closely akin to that in which they circulate in the blood.

To go back to the five variable system of Cohn, I have three slides. (Slide) The first one summarizes the advantages which accrue from fractionating plasma preparatively. First, one gets a great deal of information. If you have a plasma protein that you can work with, you can learn a great deal about it. The fact that the iron-binding globulin of plasma was isolated so that its interaction with iron could be studied, really elucidated the problem of iron transport in plasma and I think you could say something of this sort of every purified plasma protein that has been isolated. Second, it is therapeutically much more effective to fractionate plasma. If one is a clinician and interested in using blood therapeutically, it is more economical of blood, as well as of money, if one gives just what one wants. For a patient who is delivering a baby and suffers amniotic fluid infusion which defibrinates her, it is obviously more effective, and as a matter of fact, it may be effective, where nothing else will be, to give several grams of fibrinogen rather than to give a liter or more of plasma to try to accomplish the same effect. The same is true of almost any use of plasma protein, except that in a patient who is losing whole blood the use of whole blood is probably to be preferred. Third, one can keep plasma fractions longer than one can keep whole blood, and it is probably true that they can be kept longer than frozen or dried plasma because one can select the conditions of storage best for each protein. Fourth, therapeutic use of plasma fractions is safer than the use of whole plasma with respect to homologous serum hepatitis. Practically all of the fractions that are isolated can be—or I think soon will be able to be—treated in such a way that they don't transmit this virus. I think nobody is very happy about using pooled whole plasma because of hepatitis.

(Slide) This is an attempt to do a little bookkeeping of what you

could get out of 20 blood donations if you used them as dried whole plasma, forgetting the red cells for the moment. You probably could treat about 10 patients who were suffering from shock, hypoproteinemia, or another condition for which you wanted to give protein containing fluid. However, if you fractionated the same 20 donations you could probably benefit more than 100 patients treating them with the required specific fraction such as the fibrinogen in Fraction I, the gamma globulin in Fraction II, or the albumin in Fraction V. In addition, you would get some alpha globulin that you could give Dr. Bearn for starch electrophoresis at low ionic strength, and you might get a protein which Dr. Kunkel would characterize excitingly and so the investigators would be happy. Fractionation does make research into the nature of plasma proteins a great deal easier.

(Slide) The next two slides list many of the protein entities in plasma. The A/G ratio characterized plasma proteins as consisting of two fractions. Dr. Osserman told us that paper electrophoresis defines 7 or 8 components and these can be broken up somewhat further electrophoretically by the technique which Dr. Bearn described. Fractionation by the five variable system increases greatly the discrete proteins one can obtain from plasma. I don't know if one would go along with Dr. Osserman's estimate of 1000 or 2000 plasma proteins, but I would say alcohol fractionation, pushed to the limit, could perhaps isolate 100 proteins. Perhaps the method of which Dr. Ziff will tell us, will be capable of isolating considerably more unique proteins from plasma than alcohol or metal fractionation.

MODERATOR KUNKEL: Thank you, Dr. Scheinberg.

At the recent meeting, two weeks ago, of the American Chemical Society here in New York, the technique that seemed to dominate these meetings was the use of cellulose ion exchange columns, and Dr. Ziff has had considerable experience with this new tool. Perhaps he will tell us about its application to plasma proteins.

DR. ZIFF: The application of chromatography to the separation of proteins has not been as successful as it has with smaller organic molecules. First, the large size of protein molecules prevents their penetration of the adsorbent, so the adsorption must go onto sites on the surface of the adsorbing particle. This limits the amount of adsorbing surface which is available, and one needs therefore a large surface on very finely divided material for this type of chromatography.

Another factor which has made it difficult is the instability of protein itself. The latter must not be bound so strongly that when it is desorbed the internal bonds of the protein are broken, which then brings about the denaturation. There is also limitation in the eluting solvent that one can use. This of necessity is almost always aqueous and, therefore, in contrast with the situation in the chromatography of simpler materials. In spite of this, a number of adsorbents have been applied to the column chromatography of proteins. Sober and Peterson used a weak cation exchanger, Amberlite IRC50, a strong cation exchanger, Dowex 50, an anion exchanger, Dowex 2, and calcium phosphate.

I should like to go into a brief description of a system which has been used by Humphrey and Porter for the chromatography of the gamma globulin fraction.

(Slide) This shows the separation of bovine gamma globulin on a cellite column. The gamma globulin is present in a stationary aqueous phase containing urea and potassium phosphate. This is on the cellite. Through it there is a moving or mobile phase which is composed of diethyl ether of diethylene glycol. As the glycol moves through the aqueous phase, partition occurs in a sort of countercurrent distribution process on the cellite and the gamma globulin moves down the column. It is not truly column chromatography but partition chromatography. One does not obtain sharp spikes of gamma globulin but the eluate can be separated into various cuts, as shown here.

Using this technique, it was possible to demonstrate that early in immunization the hind portions of this curve contain the antibody produced and that later on it spreads out over the whole curve. Other applications have been made. The limitation of this column is that it has a small loading capacity for protein, about a milligram of protein per gram of cellite.

(Slide) Sober and Peterson have used two types of cellulose adsorbents: an anion exchanger and a cation exchanger. I won't have too much to say about the cation exchanger for lack of time. The anion exchanger is prepared by derivatizing cellulose with chloroethyl diethylamine. This compound has a substituted amino group linked to cellulose by an ether bridge. About one milliequivalent of basic group is put on per gram. This is sufficient for a fairly good loading capacity. The exchanger is positively charged in the range of neutral pH and

below, and the proteins in the form of anions are bound to the positively charged groups on the exchanger. Hence the term anion exchanger.

The cation exchanger is obtained by derivatizing the cellulose with chloracetic acid. An oxygen bridge with the cellulose results, to which a carboxymethyl group is attached. At the usual working pH this is negatively charged and binds protein by virtue of the positive charge on the protein; for this reason, it is spoken of as a cation exchanger.

To elute from the anion exchanger one starts out at weakly alkaline pH and brings the pH down. As the pH falls the dissociation of carboxyl groups on protein is repressed and they are therefore bound less extensively. The more highly negatively charged proteins have their carboxyl dissociation repressed only at the lower pH range. Thus proteins of low isoelectric point proteins tend to come off last, and in fact proteins are eluted from this exchanger in the order of decreasing isoelectric point. By a similar argument, one can show that proteins are eluted from the cation exchanger in the order of increasing isoelectric point.

(Slide) Sober and Peterson curves are shown, obtained on chromatography of horse serum on the anion exchanger accompanied by the paper electrophoretic patterns of the eluted fractions. Note that as the pH is decreased the ionic strength of the eluting buffer is increased. This helps the elution. One sees that the fractions go from gamma globulin over to albumin, and that the first to come off is gamma globulin, then beta and alpha globulin and finally albumin.

We have been working with the rheumatoid factor (or sensitized sheep cell agglutinating factor), on the anion exchanger, and the LE factor on the cation exchanger. The rheumatoid factor is present in the serum of almost all patients with rheumatoid arthritis, and the LE factor in the serum of patients with systemic lupus erythematosus.

(Slide) This gives you the pattern of a rheumatoid serum. The first peak, eluted at pH8 and 0.005 molar salt concentration, is gamma globulin. As one reduces the pH toward 5, and .15 molar salt concentration, one gets a succession of peaks and a final component that we will be interested in. In this peak (indicating), the rheumatoid factor comes off. Note that the factor comes off in a peak which is far removed from the main bulk of the gamma globulin. Nevertheless, this component is a gamma globulin, but, as has been shown by Dr. Kunkel

and his co-workers, of the macroglobulin type rather than of the usual 7S variety.

(Slide) Here is another such anion exchanger chromatogram of rheumatoid serum. Again the agglutinating activity comes off at the tail end of the chromatogram in one sharp component far removed from the main bulk of the gamma globulin.

(Slide) Here is the chromatogram of a euglobulin fraction from whole rheumatoid serum. The activity again comes off at the end.

(Slide) This is a free electrophoresis diagram of the euglobulin fraction of that hind peak. A slow and fast component are seen.

(Slide) The mobilities are both in the gamma globulin range. The factor, in other words, is a gamma globulin which is eluted at a point far removed from the main bulk of gamma globulin.

(Slide) These are ultracentrifugal patterns that Drs. Kunkel and Franklin made for us. This is the pattern of the euglobulin fraction of rheumatoid serum which has rheumatoid agglutinating activity. You see that it is mostly 7S protein, with a little 19S. After chromatography, one sees that the euglobulin fraction of the active hind peak now contains about 50 per cent of heavy component with a sedimentation coefficient of about 19. We estimate that about 90 per cent of the 7S component has been removed by fractionation on the column. The original sample which contained mostly 7S protein now is rich in heavy component. In other words, the rheumatoid factor, a macroglobulin, has been separated from the 7S gamma globulin by chromatography, because of the apparent capacity of the exchanger to separate proteins of different sedimentation coefficient.

MODERATOR KUNKEL: *We have bogged down a little in methodology and it is now time for us to deal more directly with some of the pathological disorders of serum proteins.*

Dr. Scheinberg, would you discuss briefly some of the deficiency states of serum proteins that are so prominent these days, particularly the agammaglobulinemias?

DR. SCHEINBERG: Can any of the proteins that we have heard about today be specifically absent or markedly deficient on a hereditary basis? This would be in analogy to hemophilia in which patients lack an antihemophilic factor, an antihemophilic globulin, because they possess a mutant gene which apparently is unable to synthesize, or direct the synthesis of this protein in the way that the normal allelic

gene synthesizes it. This probably can occur for any protein in the body. For example, fibrinogen and many, if not all, of the coagulation components can be absent on a hereditary basis and have been actually found to be absent because the coagulation system is relatively easy to investigate. Recently the one protein that I think everybody in this room would have thought could *not* have been absent on an hereditary basis and still allow the patient to survive has actually been reported to be absent. This is albumin. Dr. Bennhold, in Germany, saw a woman who had a slight amount of premenstrual edema and electrophoresis of her serum revealed she had no albumin whatsoever. He asked her brother to come in for examination of his blood. He of course, had very little premenstrual edema (!) but he, too, had no albumin. It is really a remarkable phenomenon that a person can walk around, can be in circulation if you will, with no albumin and apparently with normal relationships between blood and extracellular fluid. If this can be true of albumin it is probably true that absence of any protein on an hereditary basis can occur.

To take Dr. Kunkel's directions at their face value this happens to gamma globulin in a sex-linked and recessive manner. Only males get the disease known as congenital or hereditary agammaglobulinemia.

(Slide) This is a boy who was 12 years old when this slide was made. Before the age of 5 he had 8 recognized severe clinical infections, including arthritis, sinusitis, one episode of meningitis at the age of 5, and two episodes of severe pyoderma. In one of them he looked as though he was just a mass of oozing, infected skin. Antibiotics, when they came along, were ineffectual. As a matter of fact, he had more infections. Finally, when he was 9½, the syndrome, agammaglobulinemia, was recognized, largely through the work of Col. Bruton in Washington. Following regular injections of gamma globulin over the two years shown here he had almost no infections. Without gamma globulin these patients are extraordinarily susceptible to bacterial infection, although they do show some ability to develop immunity toward the viral diseases.

(Slide) The next slide is a Tiselius electrophoresis picture taken from Dr. Gitlin's article in the Scientific American this past summer. It shows rather clearly that the serum or plasma of such a patient has no gamma globulin. One of the ablest investigators in medicine today told me that he discovered this disease about 12 or 13 years ago when

he was doing a great deal of electrophoresis. He saw a plate that had no gamma globulin in it. He decided it must have been a technical error and threw the plate out without repeating it.

(Slide) The final slide shows some of the associated factors in this disease. Patients lack not only the gamma globulins associated with immunity but also the isohemagglutinins, that is, the antibodies to the antigens of red cells. These patients do not respond to immunization with bacterial antigens and show no evidence of bacterial allergy. When they are vaccinated with vaccinia virus they do develop immunity but still no gamma globulin antibody is found. Plasma cells cannot be demonstrated in their lymph nodes, and these are the cells which are usually thought to be the source of gamma globulin. This is a fascinating disease, one which shows remarkable interactions between heredity and environment and one which it is a great pleasure for the physician to meet because with gamma globulin he can make these patients normal to a degree not possible with many diseases.

DR. ZIFF: May I ask a question? Are there any conditions—maybe this is ignorance—where by heredity you find a new constituent in serum? Usually genetic abnormalities lead to missing constituents, or at least decreased amounts of normal serum constituents.

DR. SCHEINBERG: Sickle cell anemia.

DR. ZIFF: I was referring to serum.

DR. SCHEINBERG: There is some question in phenyl pyruvic oligophrenia whether phenylalanine hydroxylase is in fact absent. I don't know whether you want to call this enzyme a serum protein but at any rate there is a question as to whether or not an altered form of the enzyme may not be what is present in the disease, rather than only an absence of phenylalanine hydroxylase. If you mean an abnormal form of protein to be a new one, I don't know the answer to that. Maybe Dr. Bearn or Dr. Kunkel does.

MODERATOR KUNKEL: *That is a very good question. I think perhaps the haptoglobins—this is a peculiar term that has been appearing lately in the literature—might fit that category. Dr. Bearn might tell us something about them.*

DR. BEARN: This word "haptoglobin" is rather a cumbersome term which was first used by Jayle to designate a protein present in human serum which combines with hemoglobin. When it does so the complex is called haptoglobin. His work was largely overlooked until Smithies,

using the starch gel technique, was able to show that these haptoglobins were present in the alpha-2 fraction of serum and that individuals varied in the type of haptoglobin they possessed.

They were not quite the same in that one individual might have one haptoglobin band while others had three. He could further differentiate those that had three bands because of slightly differing mobilities. These proteins exist in all normal people and are now known to be inherited in a very characteristic genetic way. The three haptoglobin types are due to a set of two alleles without dominance. So here is yet another serum protein which is inherited in a clear-cut fashion. Though of great theoretical interest it may also be of practical value in cases of a disputed paternity.

MODERATOR KUNKEL: *Another disease that has been arousing considerable interest recently is macroglobulinemia. This was considered extremely rare but all of a sudden we are all seeing many of these cases. Dr. Osserman, could you tell us something about this disease?*

DR. OSSERMAN: You have found an epidemic of macroglobulinemia at the Rockefeller Institute because you send out those cards to the New York physicians requesting that patients with this disease be sent to the Rockefeller Institute! More properly, this is a locally endemic disease. Uptown, at the Columbia Medical Center, we have encountered only five cases of macroglobulinemia in the past four years, and have indirectly studied the serum of two other patients with this disease. Macroglobulinemia appears to be a proliferative disease of lymphocytoid-plasmacytoid origin which is related to lymphosarcoma, lymphatic leukemia and myeloma. The fully developed clinical picture is characterized by profound anemia, frequently oral and nasal bleeding, lymphadenopathy, and moderate hepatosplenomegaly. Anemia is the usual presenting complaint. Purpura, as such, is usually not a very prominent feature, as opposed to another variant of this group of dysproteinemias, idiopathic hyperglobulinemic purpura, in which the abnormal serum protein is not a macroglobulin. The marrow involved, lymph nodes and organs show diffuse infiltration with characteristically small lymphocytes and plasma cells. The small lymphocyte is virtually devoid of cytoplasm. There is evidence which indicates that both the plasma cell and the lymphocyte are capable of synthesizing globulins. Presumably, in macroglobulinemia, the abnormal lymphocyte is producing an abnormal protein akin to the myeloma protein. As mentioned be-

fore, the macroglobulin shows up electrophoretically as a sharp, homogeneous peak. It can be distinguished from the usual myeloma globulin only by ultracentrifugal analysis. Macroglobulins are insoluble in dilute salt solutions, i.e., like euglobulins. If a drop of serum from one of these patients is placed in distilled water, an immediate precipitate forms. This is the so-called Sia water dilution test. It is not specific for macroglobulinemia, and, in fact, was originally described in kala-azar, in which the euglobulin elevation gives a positive reaction.

MODERATOR KUNKEL: *I think we should now conclude this portion of the meeting and shift over to some questions that have been raised from the floor. The first one I will ask Dr. Bearn: Has the gel method of electrophoresis been of much value in differentiating the collagen disorders?*

DR. BEARN: The shortest answer is no, but I don't believe sufficient work on it has yet been done to warrant being dogmatic about it.

MODERATOR KUNKEL: *Another question: Is the albumin ever higher than normal in any disorder? Will you try that, Dr. Scheinberg?*

DR. SCHEINBERG: I don't know. The albumin can get up electrophoretically, close up to 60 per cent. I don't know whether anybody has ever described the upper limit to see whether anyone got over it.

MODERATOR KUNKEL: *This is a question for Dr. Osserman: Can individual differences be detected in normal adults by paper electrophoresis?*

DR. OSSERMAN: I am not certain about this. A few years ago Bernfeld, using free electrophoresis, described a group of normal subjects whose serum patterns showed minor differences in both shape and symmetry, particularly of the alpha globulin fractions. This was a relatively small and limited study, and I know of no further, more extensive surveys.

MODERATOR KUNKEL: *Here is a question on high voltage electrophoresis. I don't know if any of the panelists want to volunteer on this one. I think the questioner was thinking of the technique, developed by Dr. Michl in Germany, used primarily for peptides and amino acids. I don't think it comes under the serum proteins because most proteins are denatured under the conditions employed. But it is a very powerful technique for materials of lower molecular weight.*

Another question: What pH is used for the starch gel separation and what is the buffer?

DR. BEARN: Borate buffer with a pH of about 8.6 or 8.8.

MODERATOR KUNKEL: *Dr. Ziff, are the lupus factors and rheumatoid factors in the same part of the gamma globulin or are these entirely different proteins?*

DR. ZIFF: They are entirely different proteins; I don't think anybody would doubt that. They are different in their behavior on elution from the cation exchanger. Where they move in the gamma globulin fraction is open to some dispute. Some investigators have found that the rheumatoid factor moves in the more rapid portions of the gamma globulin; others have found that it moves in the middle or slower portions. The difference may be due to different degrees of purification.

The LE factor, as far as we can tell, moves in the more slowly moving portions of the gamma globulin. The two factors, of course, differ in sedimentation constant and in biological activity.

MODERATOR KUNKEL: *Dr. Osserman, do you think that the myeloma proteins represent tremendous elevations of single members of the family of normal gamma globulins?*

DR. OSSERMAN: This is a point that is still not settled. As was mentioned previously, normal gamma globulin consists of a family of a great number of different constituents. Several studies have given evidence that the normal plasma cells elaborate this wide variety of different gamma globulins. It has been postulated that, in myeloma, there is a proliferation, an abnormal growth, of one-of-a-great-many-different-plasma cells. This single family of plasma cells continues to produce a protein which is *identical* to one-of-a-great-many-*normal*-gamma-globulin components. Several physicochemical and immunochemical studies have attempted to settle this question of normalcy of the myeloma globulins, but, unfortunately, these techniques, as good as they are, cannot make this fine a distinction in protein structure and composition. Putnam's studies of the terminal amino acids of myeloma globulins and normal gamma globulin indicate that there are differences in these terminal amino acids but, again, it must be recognized that normal gamma globulin is a *mixture* of different constituents present in minute amounts. The individual gamma globulins in this fraction may conceivably differ in the arrangement and sequence of their amino acid constituents, and there may be normal n-aspartyl and n-glutamyl globulins in this heterogeneous mixture.

MODERATOR KUNKEL: *The last question: What is the significance*

of an elevation in the alpha-2 fraction, Dr. Bearn?

DR. BEARN: I was hoping Dr. Osserman was going to answer this. Although the last question, it is the hardest to answer. If one is ill from almost any cause, the alpha-2 globulins are liable to be increased. I would like to throw this question back to Dr. Osserman and ask him what he thinks an elevated alpha-2 means. I don't know, and I wish I did.

DR. OSSERMAN: I agree completely with Dr. Bearn. Alpha globulin elevation means the patient is sick. These are non-specific changes and about as significant as finding a moderately elevated sedimentation rate. A normal healthy individual should not have a high ESR, nor should he have an increase in alpha-2 globulin. This is the area of protein study which will need a great deal more exploration.

MODERATOR KUNKEL: In conclusion, I want to thank the panelists for their very fine discussion.

ROLE OF THE DRUG HOUSE IN BIOLOGICAL AND MEDICAL RESEARCH*

MAX TISHLER, PH.D.**

I SHOULD like to begin my talk on research in the History of the Drug House by quoting from a paper by Dr. L. M. McDaniel, Chairman of the Section of General Practice of the American Medical Association. Dr. McDaniel, in a paper published in the *Journal of the American Medical Association* in 1956, eloquently stated, "I remember the reluctance with which I viewed the approaching winter, for I knew that before spring fifteen patients, including several close friends, would die from pneumonia. . . . Then we felt helpless, but today we can walk into the sickroom with confidence, knowing that often a little ampule or vial half the size of one's thumb contains drugs that can conquer diseases formerly thought hopeless." With this as my text, I should like to trace briefly the growth of research in the Drug House from its small beginnings to the major force that it is today.

A number of drug houses abroad and in this country originated from apothecaries' shops that flourished during the 17th, 18th, and 19th centuries. From these shops, devoted to the preparation and dispensing of drugs, came many contributions to modern chemistry associated with such names as Scheele, Fehling, Buchner, Klaproth, Marggraf, and Pelletier. All historians of science acclaim the major and basic role of the apothecary in the creation of chemistry and also in the realization of drugs which still serve the medical profession. Among the chemical elements discovered in the apothecary shop are even uranium and zirconium, both important to our age of nuclear energy. Morphine, codeine, quinine, strychnine, and atropine, first isolated in the apothecary shop from plant drugs during the first half of the 19th century.

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are still invaluable medicinal agents. Research on drugs from plant sources—isolation, pharmacology, and chemistry—still occupies an important place in the drug house, the most notable recent illustration being the isolation of reserpine from species of rauwolfia in the Ciba Research Laboratories.

The 17th, 18th, and 19th centuries were exciting periods in the history of the physical sciences. Experimental science was widely accepted and led to the uncovering of physical laws which in some instances could predict with precision the behavior of physical bodies. This period brought to the minds of educated people the beginnings of a true respect for scientific facts. Notwithstanding this state of development in the physical sciences, the same approach in the biological and medical sciences was lacking. During this period, the *vitalist* doctrines of Bichat dominated the actions of the scientists concerned with biology and medicine. Philosophers and physicians during those times believed that life in a living organism is caused and sustained by a vital principle distinct from all physical and chemical forces as related to non-living phenomena. The beautiful and simple physical laws arising from the experimental research in chemistry, physics, and astronomy did little to stimulate biological experiments. Progress in medicine was slowed by lack of experimental inquiry and by the dogmas of vitalism.

The second half of the 19th century may be designated as the *genesis* of the experimental approach to the problems of medicine. Five men, Claude Bernard, Louis Pasteur, Robert Koch, Joseph Lister, and Paul Ehrlich, broke the chains that bound medicine to its past and unleashed a new power of research into the fields of medical sciences. Each has not only contributed handsomely to the understanding of biological processes and to the solution of medical problems, but each has left a heritage of experimental medicine which still serves as a guidepost in our ever-continuing quest for the control of disease. Bernard stated in his *Introduction to the Study of Experimental Medicine*, "Scientific medicine, like other sciences, can be established only by experimental means, i.e., by the direct and rigorous application of reasoning to the facts furnished us by observation and experiment." This declaration of Bernard's and his views on the experimental method for the study of medical problems have profoundly affected the course of medicine. Before the dawn of the 20th century, tangible contributions were already made to life and health, such as an understanding of in-

fectious diseases, aseptic surgery, safer childbirth, vaccine therapy, and sanitation.

The concept that chemicals may cure disease, first advanced by Paracelsus, began to take form in the researches of Paul Ehrlich. Dedicated to chemotherapy, Ehrlich proved by experimentation the inadequacy of von Behring's universally accepted view that "the tissues of man and animals are many times more susceptible to the poisonous effects of disinfectants than . . . any of the bacteria known." Ehrlich established the experimental procedure which gave chemotherapy a dignified and scientific stature, equal to immunology in importance and promise for the control of infectious diseases.

During these exciting years of biological and medical research, the drug house devoted most of its research to the development of production and standardization techniques for botanical and synthetic drugs. While the drug house did not contribute significantly to the developments in biology and medicine during this period, the chemical and dye industry of Germany was in a position to meet the growing challenge of chemotherapy. The introduction into medicine of salicylic acid and later aspirin, of antipyrin, of the barbiturates was the result of collaboration between the physician and the German chemical industry. Ehrlich's almost successful control of trypanosomiasis by *trypan red* and *trypan blue* and his research leading to Salvarsan for syphilis stimulated a segment of the German chemical and dye industry to enter chemotherapy with the research techniques developed in his laboratories. The time was ripe for a large-scale attack on disease through synthetic drug therapy. Biological techniques were now available and organic chemistry had begun to burst into bloom. Out of this grew institutes of chemotherapy as part of the chemical industry of which the one at Elberfeld, a part of I. G. Farbenindustries headed by Fritz Hofmann and later by Heinrich Hörlein, a student and collaborator of Paul Ehrlich, was the most notable. From these research laboratories came the antitrypanosome, tryparsamide, and the antimalarials, atebrine and plasmaquin.

Notwithstanding this new emphasis on chemotherapy, progress during the 25 years following the discovery of Salvarsan was slow and, on the whole, unrewarding. The proponents of chemotherapy could only claim a few agents for the control of the protozoal diseases and for treatment of a few non-bacterial diseases. The problem of the bacterial diseases did not respond to attack by large-scale chemotherapy, much

to the bewilderment of its investigators.

The year 1934 was the turning point for chemotherapy. Gerhard Domagk, the pathologist, working in the laboratories of I. G. Farben-industries, announced the therapeutic activity of a dye, *Prontosil Red*, in the control of experimental streptococcal infections. Chemotherapy had triumphed at last! Starting with this epochal discovery, the research laboratories of the pharmaceutical houses in Europe and in the United States synthesized many thousands of sulfonamides. Of these, a small number are of major importance in the armamentarium of the physician.

The discovery of the sulfonamide drugs had an immense influence on the more recent developments in the chemotherapy of infectious diseases, namely the discovery of the useful antibiotics. The fact that microorganisms, particularly fungi, produce substances that inhibit the growth of other microorganisms had been known by bacteriologists before Fleming chanced to observe, in 1929, the inhibitory effects of *Penicillium notatum* on staphylococci. The reinvestigation of the antibiotics for the control of infectious diseases owes its stimulation largely to the discovery of the therapeutic activity of the sulfanilamides.

In England, research in the drug house received an auspicious impetus in 1904 when Sir Henry Dale left his appointment at Cambridge University and joined the newly formed Wellcome Physiological Research Laboratories. In a delightful autobiographical sketch published in the new journal *Perspectives in Biology and Medicine*, Sir Henry Dale discussed his decision to join the Wellcome Laboratories against the advice of his friends who believed he "should be selling his scientific birthright for a mess of commercial pottage". Sir Henry Dale told how Mr. Wellcome had suggested that he should throw light on the previously obscure pharmacology of ergot; and "how, though my compliance with this suggestion had been neither eager nor hopeful, it furnished me, through a most remarkable succession of accidents and coincidences, with a series of clues, leading to my participation in nearly all the more interesting researches with which I was thereafter to be connected during the remainder of my ten years' stay in the Wellcome Laboratories, and, subsequently, during the 28 further years which I spent as a member of the staff, and eventually as the Director, of the National Institute for Medical Research."

The decade beginning with 1930 saw the introduction of *modern* research into a number of the drug companies in the United States.

Parke, Davis already had a Research Institute while Merck dedicated its Research Laboratories in 1933. In the following year, the Lilly Research Laboratories were opened and the year 1938 witnessed the dedication of the Abbott and the Squibb Research Laboratories. This was a new era for the pharmaceutical house of America. At the dedication of the Merck Research Laboratories 25 years ago, the late Mr. George W. Merck told his audience, "We believe that research work carried out with patience and persistence will bring to industry and commerce new life; and we have faith that in this new laboratory, with the tools we have supplied, science will be advanced, knowledge increased, and human life will win an even greater freedom from suffering and disease." To those who were to work in this laboratory he said, "We pledge our every aid that this enterprise shall merit the faith we have in it. Let your light so shine—that those who seek the truth, that those who toil that this world may be a better place to live in, that those who hold aloft the torch of science and knowledge through these social and economic dark ages, shall take new courage and feel their hands supported."

To the research laboratories of the pharmaceutical industry came scientists dedicated to the problems of the ill and genuinely motivated by the same ideals as those of their fellow-scientists in the universities and research institutes. With opportunities to publish their scientific findings, to present papers at scientific meetings, and to participate in all activities accorded to scientists in the universities and institutes, these men and women have gained respect and prestige. These scientists have become accepted by academic investigators on equal scientific footing. Today, the pharmaceutical industry of the United States constitutes a vital factor in our quest for better therapy, with a force of over 6,000 scientists of many disciplines and training. During the year 1957, our pharmaceutical houses spent more than $125,000,000 in support of their research. The ratio of research expenditure to total sales of the pharmaceutical industry is over twice as great as that of the chemical industry in this country.

The pharmaceutical companies recognized the need for a research organization based on active collaboration of scientists of different disciplines. With the growth of the sciences and the limitations of the human mind, specialization has become a necessity. Unlike Aristotle and Leonardo da Vinci, who did not hesitate to write definitively on *all*

sciences as well as on morals and politics, the scientists during the past half century have been carving out smaller slices as the pie grew larger. This view was recognized by Claude Bernard who stated eloquently, "The more science advances, the more she acquires an impersonal form —art is 'I', science 'we'." In organizing its research, the pharmaceutical company has brought together under a single roof scientists of different hues, all needed to carry out a program from the conceptual stage through clinical investigation. Men of different training, such as chemists, pharmacologists, pathologists, and physicians, joined together for the *first time* to collaborate in seeking solutions to medical problems. The success of this new concept of collaborative research may be illustrated by some of the accomplishments in the field of nutrition where the drug house has made a number of important and basic contributions. Research in this field had led to the isolation in the pharmaceutical houses of vitamin B_6 in 1938, of folic acid in 1947, and of vitamin B_{12} in 1948. Knowledge of the chemical structures of these vitamins and the syntheses of two demanded chemists of different skills. Nutritionists, pharmacologists, and pathologists studied the role of these vitamins in the nutrition of animals, whereas the importance of these vitamins in human health required collaboration with physicians. It is likely that several hundred scientists in the pharmaceutical industry, representing a great many scientific disciplines, participated in the research which established these vitamins and their place in nutrition.

The establishment of these research laboratories encouraged academic and clinical investigators to seek assistance of, and frequently collaboration with, the scientists of the pharmaceutical companies in the prosecution of their research and in transforming the results of research into useful tools for the physician. Many of our important contributions have resulted from such collaborations. After the initial announcement by Banting, McLeod, Best, and Collip of the discovery of insulin, their collaboration with the Lilly research staff resulted in a suitable product for use by the physician. Lilly's and Lederle's initial liver preparations originated from a collaboration with Minot and Murphy. Putnam and Merritt established the usefulness of Dilantin in the treatment of epilepsy as a consequence of a collaboration with Parke, Davis. Paul R. Burkholder of Yale furnished Parke, Davis isolates of microorganisms which eventuated in the discovery of Chloromycetin. A collaboration between E. B. Astwood, now at Tufts Medical School, and Lederle

led to the discovery of the antithyroid activity of thiouracil and propyl thiouracil. The structures and syntheses of vitamin B_1 and of pantothenic acid were the consequences of collaboration between Merck scientists and R. R. Williams and R. J. Williams, respectively. The importance of cortisone in therapy was *negligible* until Philip S. Hench of the Mayo Clinic, prompted by his own concepts, discovered the usefulness of cortisone in the treatment of rheumatoid arthritis. This observation, which ushered us into a new aurora of research and therapy and for which Dr. Hench was accorded the Nobel Prize, was made with cortisone synthesized for the first time in the Merck Research Laboratories.

Research in the pharmaceutical house has been both *basic* and *developmental* in nature. This combination of talents directed at specific objectives accounts for the rapid and efficient utilization of breakthroughs in modern therapy whether the breakthroughs occur in the industry or in the laboratories of outside scientists. When a successful penetration into a new area of research is made, the modern pharmaceutical house is superbly able to muster its forces and pursue the thrust to practical advantage. Ehrlich's demonstration of methods for studying infectious diseases and of their potential value in the search for new agents had been taken over and elegantly elaborated by the pharmaceutical industry. The discovery of tyrothricin in 1939 by René J. Dubos of the Rockefeller Institute, through his thoughtful study of the physiology of microorganisms and problems of antagonisms, the discovery of the therapeutic value of penicillin in 1940 by Chain, Florey, Gardner, and Heatley, and Waksman's researches leading to streptomycin, unleashed powerful forces in the drug companies which led to the discovery of the broad-spectra antibiotics. The discovery of the psychopharmacodynamic effect of chlorpromazine quickly brought into being an entirely new kind of pharmacology laboratory in the industry which has already served in the development of a number of new agents with different actions for the control of mental disturbances. Polio vaccine, which owes its creation to the work of John F. Enders and of Jonas Salk, brought tissue culture techniques and a resurgence of interest in immunology to the pharmaceutical industry.

The situation in the pharmaceutical industry today is quite different from that of 20 years ago. Every drug company of size has a research organization capable of making new and important contributions. Each company must have a research group to grow or even to survive.

Obsolescence in therapy has become a major characteristic of the age in which we live. Actually, research in the pharmaceutical company generates obsolescence and to a degree, one of its aims is planned obsolescence, whereby an inadequate therapeutic agent is replaced by a better one. Most of us remember how the introduction of prednisone by Schering quickly overshadowed cortisone and hydrocortisone for the treatment of the inflammatory diseases. Aureomycin, discovered in the Lederle Laboratories, and Terramycin, first isolated by the Pfizer research staff, rapidly lost their pre-eminence in the broad-spectra antibiotic field to the closely related tetracycline. In the recent past, the arsenicals, including the arsphenamide derivatives, once major therapeutic agents, have passed into oblivion. Therapy with immune sera, once a major hope in the control of the bacterial infectious diseases, rapidly yielded to the sulfonamides and to the antibiotics.

In line with the theme of this symposium, I have stressed, thus far, the research but not the development and production activities of the pharmaceutical industry. These latter segments have played a vital part in our history, particularly since the drugs of the past quarter century have become more complicated in chemical structure and properties than ever before. Chemists and engineers, employing at first the techniques and equipment of the chemical industry and later developing newer ones of their own, have narrowed the gap of time between the research investigator and the physician. The speed with which penicillin and streptomycin were brought to the physician in unlimited quantities, and at low prices, is unsurpassed by the most notable developments in other industries. Within a period of 18 months following the establishment of the usefulness of the polio vaccine, supplies were plentiful. The Asiatic influenza vaccine was in abundance four months after the causative virus was made available to the pharmaceutical industry by the National Institutes of Health.

One of the objectives of the development and production arms of the drug industry is the constant improvement of production processes with the lowering of production costs and the lowering of prices to the patient. In spite of the economic inflation of our times, the prices of most basic drugs have decreased over the years. An examination of the prices today of those pharmaceuticals in use 10 or even 20 years ago will reveal a continual and significant reduction in most prices in spite of the cost increases of labor, facilities, taxes, etc. Typical examples of

this price history are the vitamins, the sulfa drugs, and the antibiotics, penicillin and streptomycin. These significant reductions have resulted from technical achievements and are a tribute to the pharmaceutical industry for its wisdom and dedication.

No account of the pharmaceutical industry is complete without discussing the development of Government-sponsored research and its impact on the industry. Beginning with the demands of World War II, research carried out in Government laboratories and research supported financially in other laboratories have become a formidable force growing rapidly with each passing year. Today, the military services, the Public Health Service, and the National Science Foundation are the major patrons of the laboratories in our colleges and universities. As much as two-thirds of the expenditures for all research and development performed in the academic laboratories is financed by the Federal Government.

The acceleration of Government-supported research has manifested itself in the rapid growth of the National Institutes of Health, the research arm of the Public Health Service. Beginning in 1930 as one institute, devoted to the investigation of infectious diseases, it now consists of seven institutes charged with the responsibilities of distributing financial assistance to academic and institute investigators and of carrying out research in the areas defined by each of its institutes. The budget for the National Institutes of Health has grown from 52 million in 1950 to 211 million in 1958, surpassing the expenditures for research by the pharmaceutical industry. This significant development constitutes a new factor which will play an important part in the medical advances of the future. For example, the problem of cancer has prompted the organization of the Cancer Chemotherapy National Service Center as part of the National Institutes of Health for the purpose of seeking substances which will contain the neoplastic diseases. This Center has actively sought the aid of the drug house and has actually issued contracts to some with provisions for financial assistance. For the first time, a Government agency has been directed to set up a research program during peacetime on a national scale, with Government financial support, aimed at the control of a specific disease. Now that this program is under way, there are signs that similar projects will be formulated in the field of mental health and in the field of the cardiovascular diseases.

The entrance of the Government into research on a grand scale for the control of specific diseases poses a problem for all those engaged in medical research on how to deploy most effectively the people, the funds, and facilities. It would be wrong and wasteful for the Federal agencies to take over those activities being handled with proven adequacy by others, and here I mean the private investigators, universities and research institutes, as well as the pharmaceutical industry.

The pharmaceutical company, with its technical staff and skills, is admirably capable of participating in breakthroughs and bringing them to speedy realization. With its scientists and engineers, the pharmaceutical industry has contracted the path from breakthrough to the physician, notwithstanding the increasing complexity of the technological problems.

Our true capacity to advance in the medical sciences will depend on the depth of our understanding of the fundamentals which underlie our knowledge of biological and medical facts. In spite of the remarkable progress in the biological and medical sciences, our understanding of fundamentals is woefully inadequate. While we can perform reactions that are almost miracles and even can improve on nature, we are unable to answer many of the simplest questions raised from scientific observations in the medical sciences. While we can synthesize hormones and know how to use them in allaying disease, we do not know how they act. When we begin to understand what goes on at the cellular level, our contributions to control disease will be broader and more permanent.

The pace of progress during the past 25 years in the medical sciences cannot be accelerated unless we have a much better understanding of the fundamentals of medical sciences. To fill the glaring gaps in our knowledge, we need an enormous re-orientation of our scientific effort into long-range, undirected, basic research. We need to support basic research with all the facilities and funds that can be absorbed. It is in this area of greatest deficiency that the drug house has been unable to make a significant contribution. The pharmaceutical industry is limited in capacity to carry out basic research and in ability to provide it with adequate financial support. It is in this endeavor that Government assistance and encouragement are urgently needed. Lack of Government and public support for long-range, basic research in favor of the more immediate and applied research would bring about a sterile and stagnant future, devoid of major advances which, as scientists, we know should

be achieved over the next 25 years.

We have come a long way from the drug house and apothecary shop of three centuries ago. We stand on the crest of a golden age in the medical sciences viewing beyond a more towering and noble summit. The dream of the Fountain of Youth is taking form in reality and the search for the philosopher's stone is no longer an idle quest. The accomplishments during the past quarter century have given us the strength and inspiration to meet the challenges of the years ahead. Let us not falter in our responsibilities.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACT OF PAPER AND DISCUSSION

Presented at the Meeting on October 23, 1958 at The New York Academy of Medicine

Involvement of the Nervous System by Bronchogenic Carcinoma

WILLIAM HENRY MCMENEMEY

Institute of Neurology of the University of London,
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Dr. McMenemey discussed the incidence of bronchial carcinoma in different types of hospitals, comparing published figures with his own. Comparison was often difficult because melanoma was sometimes included and sometimes not. In his own series, in which melanocarcinoma had been included, a bronchial origin was established in 52.5 per cent of cases. In a neurological hospital the primary tumor is usually silent and the search for it both clinically and at necropsy may prove difficult. Unless the histologic diagnosis has been established beyond doubt in a case of cerebral tumor, the lungs, after routine examination at necropsy, should be preserved for more detailed studies in case the diagnosis proves to be one of metastatic carcinoma of the brain. The association of metastases in the adrenals and brain was suggestive of a primary site in the lung, especially in a male. The speaker compared present-day statistics with earlier ones, more especially those of Krasting (1906)[1], and concluded that there had been a definite increase in the disease.

The symptomatology of carcinomatous involvement of the nervous system, he said, was protean, and the disease might present in many unusual ways. He gave several examples, including one which first showed as a cerebellar hemorrhage and another as an acute cauda equina syndrome. The clinical course of a bronchial metastasis in the brain might at times be so slow as to throw doubt on the diagnosis. Dr. McMenemey drew attention to the frequency with which the meninges were involved, sometimes without any obvious discrete secondary tumor being present in the brain. He and his colleague, Dr. J. N. Cumings, in a large series of cases of histologically confirmed tumor of the brain, had noticed that the cerebrospinal fluid cell count was raised above 5 in 20.4 per cent of cases of intracranial carcinoma, over 10 in 15.3 per cent, and over 20 in 8.5 per cent. Very often tumor cells could be identified. On occasion they had been found when the total cell count was within the normal range. If, therefore, a diagnosis of carcinomatosis of the brain were under consideration, a search of the deposit for the presence of carcinoma cells was always worth while. The significance of a falling glucose content in the cerebrospinal fluid was also discussed.

Dr. McMenemey described the findings in three cases of cerebellar degeneration in association with carcinoma, a rare but important combination. However, its incidence was sometimes underestimated because in a very sick person cerebellar symptoms and signs might not be easily apparent. In general the disease seemed to be associated with small primary tumors, and metastases in the brain and elsewhere were more often absent than present. He described also examples of

carcinomatous neuropathy, pointing out that in this disease, as well as in cerebellar degeneration, the degeneration did not proceed *pari passu* with the growth of the primary tumor. The presence of either cerebellar degeneration or a carcinomatous neuropathy in a previously well patient should encourage a hunt for a primary tumor. The speaker then discussed the possibility of there being a specific form of cortical degeneration associated with the presence of carcinoma, and instanced the work of Brierley and Charatan (1956)[3]. He discussed the significance in cerebellar degeneration of the lymphocytic infiltration sometimes found; also a first zone Lange curve. Finally, he compared the incidence of bronchial carcinoma in Britain with that in the United States, concluding that it was not smoking alone, nor atmospheric pollution alone which accounted for the prevalence of the disease, but a summation of insults to the bronchial mucosa associated with civilization. To discourage smoking was the one quick way of reducing the insult, and at the same time, of diminishing the alarmingly increased incidence of the disease.

DISCUSSION

JOHN G. KIDD: A few years ago I lent Dr. Willis' book, *The Spread of Tumors*, to one of my students. When I asked him what he got out of it, he said that he could summarize the whole book in a single sentence: "A tumor arises anywhere in the body, and spreads anywhere in the body." What we have seen this evening is that bronchogenic carcinomas have the capacity to spread not only to the brain, but to other parts of the nervous system under circumstances that are little short of bizarre. Dr. Zimmerman, a distinguished member of our Society, is in the audience. Since he has had wide experience in lesions of the central nervous system, I wonder whether he would be good enough to give us his evaluation of his own experience in comparison with this of Dr. McMenemey.

HARRY M. ZIMMERMAN: All of us know Dr. McMenemey as a neuropathologist and as the superb architect of the International Neuropathological Congress in London, which some of us in this audience will never forget. This is a marvellous opportunity for those who are general pathologists to compare notes with you, Dr. McMenemey, since you are both a general pathologist and a neuropathologist. I have a few questions to ask you. One is, how often have you seen carcinoma in cases of multiple sclerosis? This is a question I have been asked innumerable times by such people as Hans Reese in this country and others interested in multiple sclerosis, following a statement by Schaltenbrand of Germany to the effect that the two diseases are incompatible. I was therefore astonished to find in our Multiple Sclerosis Registry, which we carry on at our Hospital, that 8 to 10 per cent of cases of multiple sclerosis have carcinoma of one organ or another, not necessarily of the lung.

The remark that Dr. Kidd made that tumors may arise anywhere and go anywhere (and the lung is one of these organs) brings to mind the fact that in our experience, and in yours, carcinoma of the lung is by far the most frequent primary site of central nervous system metastases. In some 1400 cases of pulmonary carcinoma we had, I believe, several hundred which went to the brain, which is by all odds the most frequent site of metastasis from any primary carcinoma anywhere in the body. Next in frequency in our hospital is breast carcinoma, but unlike the pulmonary carcinomas, the breast tumors go to the intracranial dura and to the spinal dura much more frequently than they do to the parenchyma of the central nervous system.

There are a few other things that Dr. Kidd's remark brought to my attention. We have seen a number of cases of carcinoma of the urinary bladder with metastases to the brain, and almost invariably when apparently primary metastases occur in these odd sites there is an intermediate station in the lung. We have found repeatedly that a bizarre type of tumor, one that rarely goes to the brain, when it does so, almost always goes by way of an intermediate station in the lung.

You have not mentioned, Dr. McMenemey, malignant lymphomas of the nervous sys-

tem, and I am not referring to those associated necessarily with malignant lymphoma in the bone marrow or lymph nodes. I have now some 16 cases of primary lymphoma in the central nervous system, among them reticulum cell sarcomas, lymphosarcomas, Hodgkin's disease, and so forth. Do you see them in your collection?

LIONEL S. AUSTER: Inasmuch as my avocation is that of a pathologist, and my true vocation is that of a surgeon interested in tumor pathology, perhaps you will bear with me for a moment, because Dr. McMenemey's magnificent array of material, in spite of the fact that his title did not limit involvement, nevertheless was almost exclusively shown in the brain. In at least one instance he was able to show some posterior nerve root involvement as evidence of peripheral neuropathy, and I should like not only to call attention to this group, but to request help and information to explain the reason for a most important symptomatic aspect of morbidity in pulmonary carcinoma: the neuralgia or neuropathy producing pain incidental to lesions found more particularly in the upper lobe, the so-called sulcus tumors. These notoriously produce bizarre, seemingly unrelated symptoms even before there is demonstrable evidence of true pulmonary parenchymatous involvement. I have seen in my own scant personal experience at least half a dozen cases in which the paresis of one vocal cord plus a peculiar irritative cough is the only early symptom, without anything else that might help one to suspect the presence of an upper lobe tumor. Another sign is the Horner syndrome. Moreover, there is a type of upper lobe tumor which very rapidly involves the upper and posterior mediastinum, with erosion of the anterior surface of the vertebral bodies, affecting, strangely enough, not the anterior roots, but the posterior spinal nerve roots, with severe pain referable to C-6 and 7 and T-1, 2 and 3, and radiation to the neck, the shoulder, and axilla. The cause is eventually, after a long time, demonstrable as a lesion arising from the lung and in the upper posterior mediastinum. Only after the most detailed roentgen studies in the oblique position will such erosion and bone involvement sometimes show. For relief of pain these patients receive high dosage radiation therapy, and now, with the advent of cobalt therapy, relief is better than previously. But they are never completely relieved, despite occasional shrinkage of the tumor. As Dr. Sala and I showed in a study of the causes of death in cancer of the cervix[2], and a similar situation is seen in cancer of the prostate, after extensive radiation therapy without any evidence of residual tumor in or about the primary sites, there is not only a contraction as a result of fibrosis, but also persistence of carcinoma in the periureteral and perineural lymphatics in the pelvis and lower abdomen, which accounts for the pain. I wonder whether anyone has seen, or has had the opportunity to dissect, posterior nerve roots in lung cancer cases to see why it is that these patients have persistent pain which is subjectively far worse than that caused by the essential primary lesion.

I believe perineural lymphatic involvement is the answer.

In connection with the reported excess of pulmonary carcinoma prevalent in the United Kingdom compared with that in the United States, I am also tempted to state that perhaps one of the reasons is that the British make those extremely irritating and highly carcinogenic types of cigarettes that are made from pure Virginia tobacco.

WILLIAM H. McMENEMEY: In reply to Dr. Zimmerman's question concerning the coexistence of carcinoma with multiple sclerosis, I can only recall one case, many years ago. I think that most cases of multiple sclerosis die before they get into the carcinoma age group. That may be one reason, but we do not get many bodies for postmortem showing the pathology of multiple sclerosis. More usually we receive only the brain and cord, with the information that a complete necropsy has been carried out and nothing else found. I am much interested to hear your experience concerning this association. I agree absolutely about carcinoma of the breast and its tendency to involve the dura. It is very striking in many of the ones we have had. I have seen only one instance of carcinoma of the

bladder metastasizing to the brain, and I cannot recall whether there was a lesion of the lung, but I would expect that there was.

We have had some cases of malignant lymphoma, but they have mostly been lesions of the cord; we have had a few instances, however, of reticulum cell sarcoma involving the brain.

In reply to Dr. Auster, the so-called Pancoast syndrome, I think, is the one you mean. I have not had any for some years—not since I have been working in a neurological hospital, but I do remember having seen them previously at another hospital. I believe they had pain, but the roots were not studied microscopically. I am grateful for your remarks and agree that these cases would repay more detailed study.

MORRIS F. WIENER: Is it feasible to routinely examine the spinal fluid for malignant cells in all cases of bronchogenic carcinoma, especially where radical surgery is contemplated? This question is suggested by the purported high incidence of central nervous system involvement in carcinoma of the lung.

WILLIAM H. McMENEMEY: Yes, if there are the slightest clinical grounds for believing that the central nervous system is already involved.

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OCTOBER 5 to 9, 1959

RESEARCH CONTRIBUTIONS TO CLINICAL PRACTICE

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THIRD ANNUAL POSTGRADUATE WEEK

OCTOBER 5 to 9, 1959

RESEARCH CONTRIBUTIONS TO CLINICAL PRACTICE

PANEL MEETING — 4 P.M.

Monday October 5

PHYSIOLOGY AND THERAPY OF THE GASTRECTOMIZED PATIENT

Chairman: THOMAS P. ALMY, *Cornell University Medical College*

LECTURES — 8:30 P.M.

CONTRIBUTIONS OF MOLECULAR BIOLOGY TO MEDICINE

FRANCIS O. SCHMITT, *Massachusetts Institute of Technology*

THE ESSENTIAL NATURE OF GLYCINE IN THE DYNAMICS OF THE CELL

DAVID RITTENBERG, Ph.D., *College of Physicians and Surgeons, Columbia University*

PANEL MEETING — 4 P.M.

Tuesday October 6

LONG-TERM RESULTS OF SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

Chairman: CHARLES E. KOSSMANN, *New York University College of Medicine*

LECTURES — 8:30 P.M.

FACTORS INVOLVED IN CAUSING CONGENITAL MALFORMATIONS

JAMES G. WILSON, *University of Florida College of Medicine*

ADRENOGENITAL SYNDROME: ITS CAUSES, MANIFESTATIONS AND TREATMENT

LAWSON WILKINS, *The Johns Hopkins University School of Medicine*

CONTRIBUTIONS OF PNEUMOCOCCAL GENETICS TO FUNDAMENTAL PROBLEMS IN BIOLOGY

ROBERT AUSTRIAN, *State University of New York, Downstate Medical Center*

PANEL MEETING — 4 P.M.

Wednesday October 7

IATROGENICALLY INDUCED LIVER DISEASE

Chairman: GERALD KLATSKIN, *Yale University School of Medicine*

LECTURES — 8:30 P.M.

CELLULAR EFFECTS OF IONIZING RADIATION

HENRY S. KAPLAN, *Stanford University School of Medicine*

(continued on following page)

LECTURES — 8:30 P.M. (continued)

Wednesday October 7 *(continued)*

NEWER METABOLIC ASPECTS OF TRAUMA
JOHN M. KINNEY, *Harvard Medical School*

THE RELATION OF ENDOTOXIN TO FEVER AND SHOCK
CHANDLER A. STETSON, JR., *New York University College of Medicine*

PANEL MEETING — 4 P.M.

Thursday October 8

FERTILITY AND INFERTILITY
Chairman: JOHN ROCK, *Harvard Medical School*

LECTURES — 8:30 P.M.

GLYCOLYTIC PATHWAYS AND THEIR RELATIONSHIP TO LIPID METABOLISM
MARVIN D. SIPERSTEIN, *The University of Texas, Southwestern Medical School*

THE METABOLISM OF THE SERUM LIPOPROTEINS AND ITS RELATIONSHIP TO ATHEROSCLEROSIS
HOWARD A. EDER, *Albert Einstein College of Medicine*

THE PRESENT STATUS OF THE DIETARY FAT-SERUM LIPID PROBLEM
EDWARD H. AHRENS, *Jr., The Rockefeller Institute*

PANEL MEETING — 4 P.M.

Friday October 9

PROBLEMS IN HYPERSENSITIVITY
Chairman: H. SHERWOOD LAWRENCE, *New York University College of Medicine*

LECTURES — 8:30 P.M.

COPPER METABOLISM AND CERULOPLASMIN
I. HERBERT SCHEINBERG, *Albert Einstein College of Medicine*

IRON METABOLISM AND THE PATHOGENESIS OF IRON DEFICIENCY ANEMIA
CARL V. MOORE, *Washington University School of Medicine*

THE METABOLISM AND THE INTESTINAL TRANSPORT OF CALCIUM
DAVID SCHACHTER, *College of Physicians and Surgeons, Columbia University*

SCIENTIFIC EXHIBIT

The Scientific Exhibit will open officially at 11 a.m. WEDNESDAY, SEPTEMBER 30, 1959 and be open daily 10 a.m. to 10 p.m. through October 9, except Saturday and Sunday, October 3 and 4.

MONTHLY PANEL MEETINGS FOR THE GENERAL PHYSICIAN

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(Please note: For this academic year there will be a change in the time and the day of these meetings. Panels will be held **evenings** *on the THIRD THURSDAY of the month, at* **9:00 p.m.**, *in Room 20 at the Academy.)*

THURSDAY November 19 1959	THE USE OF ORAL HYPOGLYCEMIC AGENTS *Moderator:* EDWARD TOLSTOI
THURSDAY December 17 1959	CURRENT CONCEPTS IN THE TREATMENT OF COMMON CONGENITAL HEART DEFECTS *Moderator:* JERE W. LORD, JR.
THURSDAY January 21 1960	THE FUNCTIONS OF THE HOSPITAL EMERGENCY ROOM *Moderator:* PRESTON A. WADE
THURSDAY February 18 1960	MANAGEMENT OF ALLERGIC STATES *Moderator:* HORACE S. BALDWIN
THURSDAY March 17 1960	TREATMENT OF COMMON POISONS *Moderator:* HAROLD JACOBZINER
THURSDAY April 21 1960	PATHOGENESIS AND MANAGEMENT OF ASCITES *Moderator:* FRANKLIN M. HANGER

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TUESDAY, OCTOBER 27, 1959

to be held at

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MORNING SESSION

THE PROTEIN NUTRITION OF INFANTS

Dr. Samuel Z. Levine, *Moderator, Professor of Pediatrics, Cornell University Medical College and Pediatrician-in-Chief, The New York Hospital*

8:30	*Registration*
9:00	*Welcome*—Dr. Joseph C. Hinsey, *Director, The New York Hospital-Cornell Medical Center*
9:15	*Introduction*—Dr. Levine
9:25-11:00	AMINO ACID REQUIREMENTS OF INFANTS—Dr. L. Emmett Holt, Jr., *Professor of Pediatrics, New York University College of Medicine*
	DIFFERENCES IN HUMAN AND COW'S MILK—Dr. Harold H. Williams, *Professor of Biochemistry and Nutrition, Cornell University*
	PROTEIN ALLOWANCES FOR PREMATURE INFANTS—Dr. Harry H. Gordon, *Pediatrician-in-Chief, Sinai Hospital of Baltimore*
	PROTEIN ALLOWANCES FOR FULL-TERM INFANTS—Dr. Calvin W. Woodruff, *Associate Professor of Pediatrics, School of Medicine, Vanderbilt University*
11:00-11:15	Recess
11:15-12:30	Panel Discussion
	Dr. Moises Béhar, *Chief, Clinical Investigations, Institute of Nutrition of Central America and Panama*
	Dr. Paul György, *Professor of Pediatrics, University of Pennsylvania School of Medicine*
	Dr. William M. Wallace, *Professor of Pediatrics, Western Reserve University School of Medicine*
	and
	Doctors Gordon, Holt, Williams and Woodruff

EVENING SESSION — 8:00-10:00 p.m.

Dr. Robert L. Jackson, *Moderator, Professor of Pediatrics, University of Missouri*

APPETITE REGULATION IN THE YOUNG—Dr. John R. Brobeck, *Professor of Physiology, University of Pennsylvania*

IRON REQUIREMENTS OF THE INFANT—Dr. Irving Schulman, *Professor of Pediatrics, Northwestern University Medical School*

CLINICAL MANIFESTATIONS OF GENETIC ABERRATIONS OF CALCIUM AND PHOSPHORUS METABOLISM—Dr. Donald Fraser, *Associate Professor of Pediatrics, University of Toronto Faculty of Medicine, Canada*

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The New York Academy of Medicine has entered into an agreement with University Microfilms, Ann Arbor, Michigan, to make available to libraries issues of *The Bulletin* in microfilm form.

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A major advance in the treatment of mental depression came with a newer understanding of the influence of brain serotonin and norepinephrine on the mood. Levels of both these neurohormones are decreased in animals under experimental conditions analogous to depression; relief of these model depressions is seen with a rise in the levels of both serotonin and norepinephrine.

A second advance came with the development of monoamine oxidase inhibitors, substances which raise the cerebral level of both serotonin and norepinephrine. The first of the amine oxidase inhibitors raised the cerebral level of serotonin, but did not appear to raise norepinephrine levels proportionately.

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References

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Freis, E.D.: J.A.M.A. 169:105, (Jan. 10) 1959.

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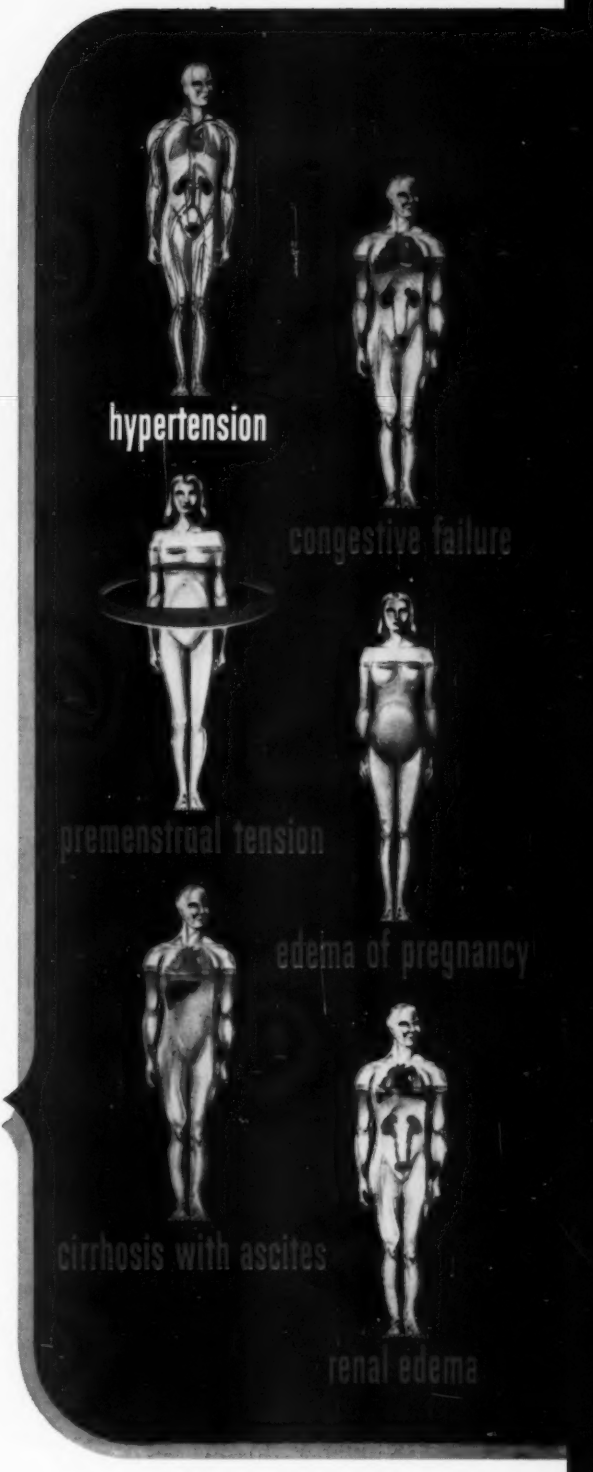

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September 3—THE DEVELOPMENT AND USE OF THE PROTHROMBIN—Armand J. Quick, *Professor of Biochemistry, and Director of the Department, Marquette University School of Medicine, Milwaukee, Wis.*

THE DISCOVERY AND PHYSIOLOGICAL PROPERTIES OF DICUMAROL AND OTHER COUMARIN DERIVATIVES—Karl Paul Link, *Professor of Biochemistry, University of Wisconsin*

September 10—HEPATIC COMA—Sidney Liebowitz, *Physician, Beth Israel Hospital, New York City*

DERMABRASION—Douglas Torre, *Assistant Dermatologist, Memorial Hospital, New York City*

September 17—HEPATIC CIRCULATORY PHYSIOLOGY—Stanley E. Bradley, *Professor of Medicine, College of Physicians and Surgeons, Columbia University*

JAUNDICE AND BILIRUBIN METABOLISM — Rudi Schmid, *Associate in Medicine, Harvard Medical School*

September 24—MANAGEMENT OF PORTAL HYPERTENSION — Arthur B. Voorhees, Jr., *Assistant Attending Surgeon, Columbia Presbyterian Medical Center*

EMOTION AND CARDIOVASCULAR DISEASE—Burton L. Zohman, *Clinical Professor of Medicine, State University College of Medicine, Brooklyn, N. Y.*

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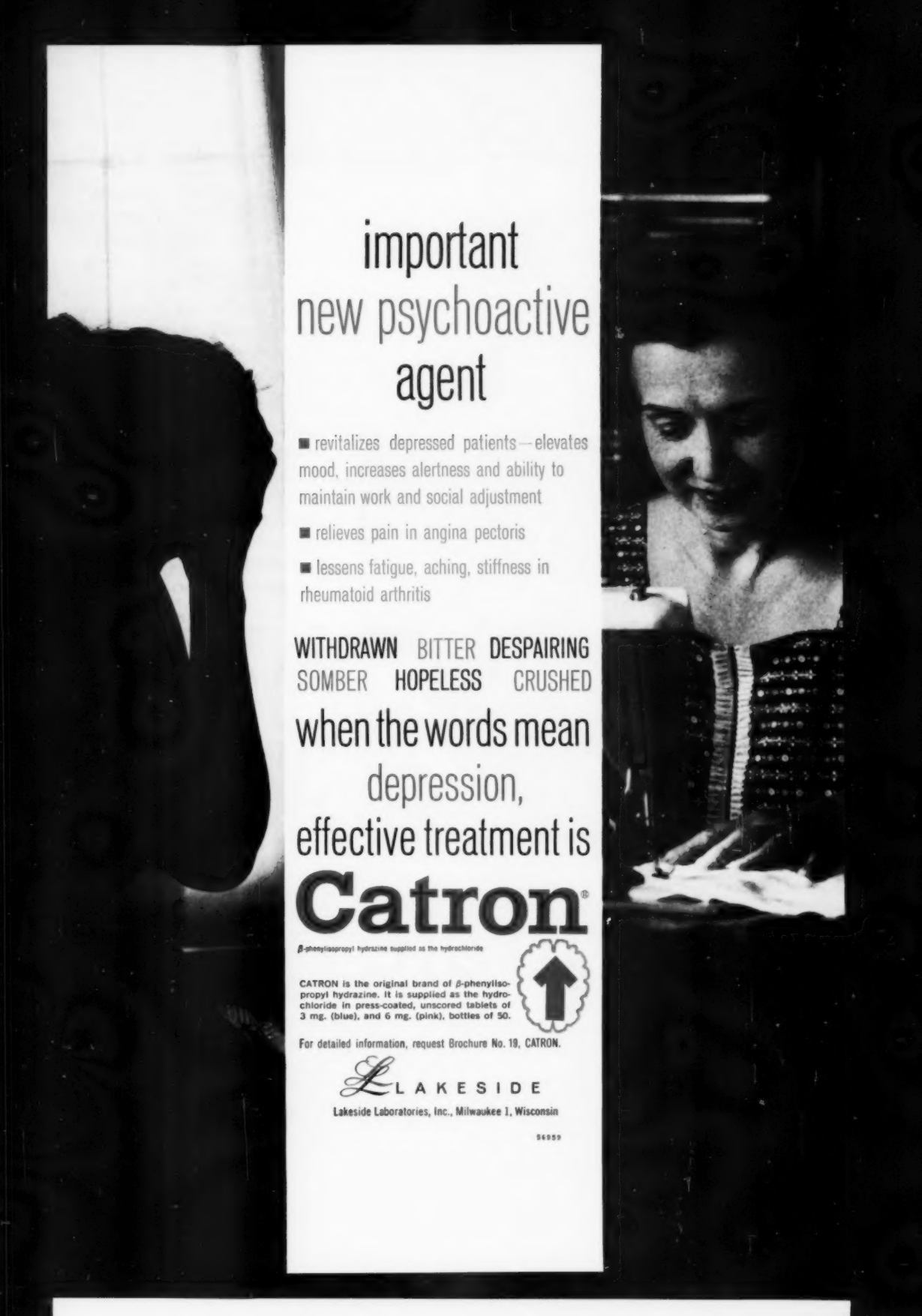

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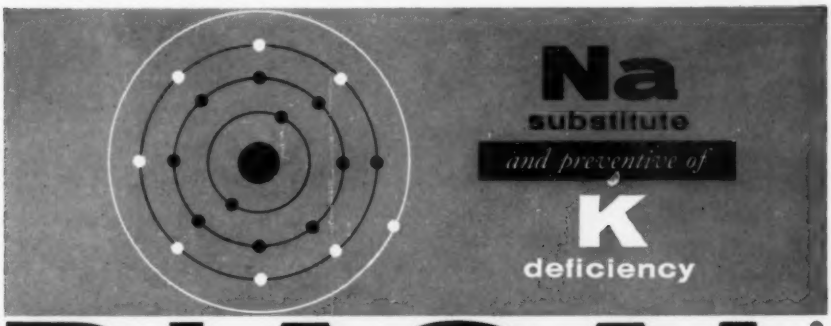

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TRICOFURON®

Improved

■ Swiftly relieves itching, burning, malodor and leukorrhea ■ Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing

2 steps to lasting relief:

1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

NITROFURANS—a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK

Many **MIGRAINE** attacks can be **stopped at the start** by the prompt use of...

'MIGRAL'®

Advantage

'MIGRAL' permits maximum ergotamine therapy with the first dose —because the 'MIGRAL' formula includes the proved antiemetic, cyclizine hydrochloride, to counteract the tendency to nausea and vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

In bottles of 20 and 100 tablets.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

versatility

Either as food or as medicine, more physicians are finding wider application of DANNON* YOGURT in their daily practice... it fits into practically any regimen.

nutritionally...

• Dannon Yogurt provides a delicious, palatable source of protein-mineral supply; it is low in calories (50% butter fat removed), a natural, good-tasting food supplement, smooth as custard, in several palate-tested flavors... plain, orange, strawberry, vanilla and prune whip. Simply excellent for all ages.

medicinally...

• Dannon Yogurt is a valuable, physiological adjunct in the treatment of gastrointestinal dysfunction, diarrhea, autointoxication, flatulence, obesity, in the correction of faulty eating habits. In chronic constipation, Dannon Prune Whip Yogurt has been found 95% effective when taken every night before bedtime for three weeks*.

try it, doctor...

• either on several hard-to-manage patients, or in your own home. We should be pleased to send a supply of introductory coupons to you and to any patients you may designate.

*Feuer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:273, 1955
Write for reprints

DANNON MILK PRODUCTS INC., 22-11 38th AVENUE, LONG ISLAND CITY 1 N. Y.